Biological Network Modelling

Relating Structure and Dynamics to Function in Food Webs and Neural Networks

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Abstract

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This study takes a network approach to understanding complex biological systems. The overall objective is to explore how the stability and flexibility of biological networks emerge from underlying structural and dynamical characteristics. The thesis is arranged as a journey into the complexity of biological network models. The starting point is qualitative structural network descriptions. The level of detail in the dynamical description of node properties is then gradually increased. Along this journey, new features, both structural and dynamical, are revealed as crucial for the function of biological networks.

A set of constructional properties are defined: s*tructural principles, structural complexity, interaction diversity, node diversity* and *network density*. These constructional properties capture important aspects of the structural organization and dynamic mechanisms in biological networks. A set of functional properties are defined: *structural robustness, structural cyclicity, dynamic stability* and *dynamic flexibility*. These functional properties are systemic properties that are all related to the stability of biological networks. These two sets of properties are used to demonstrate how the construction of biological networks is crucial for their function. The general theory is applied to food web and neural network models, where the general network properties are given specific biological meanings. The studies within both fields have their system specific objectives.

A simple food web model is developed for explicitly including a compartment for dead organic material (detritus). Several constructional properties are revealed as crucial for the structural robustness, the structural cyclicity and the dynamic stability of food webs. The pathways due to decomposing and recycling of detritus alter the constructional properties, and are crucial for food web function.

Computational neural network models are developed for clinical applications. Possible mechanisms behind electroconvulsive treatment (ECT) and anaesthetics are modelled. Clinical observations are qualitatively reproduced. Several aspects of the constructional properties of neural networks are revealed as crucial for optimal stability and flexibility of neurodynamics.

Keywords: network theory, system analysis, biological network, food web, neural network, neurodynamics, stability, flexibility, EEG, modified niche model, detritus, network density.

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(Halnes 2007)

List of papers

Paper I: Geir Halnes, Brian Fath & Hans Liljenström 2007. The Modified Niche Model: Including Detritus in Simple Structural Food Web Models. *Ecological Modelling 208*, 9-16.

Paper II: Brian Fath & Geir Halnes 2007. Cyclic Energy Pathways in Ecological Food Webs. *Ecological Modelling 208*, 17-24.

Paper III: Geir Halnes 2007. The Effect of Food Web Structure and Interaction Strength Distribution on the Stability of Ecosystem- and Food Web Models. *(Manuscript)*.

Paper IV: Yuqiao Gu, Geir Halnes, Hans Liljenström & Björn Wahlund 2004. A Cortical Network Model for Clinical EEG Data Analysis. *Neurocomputing 58-60*, 1187-1196.

Paper V: Geir Halnes, Hans Liljenström & Peter Århem 2007. Density Dependent Neurodynamics. *BioSystems 89*, 126-134.

Notes on the authorships

Paper I: The outline of the project was determined by Halnes and Fath. All work on modelling and simulations by Halnes. The paper was mainly written by Halnes with useful comments by Fath and Liljenström.

Paper II: The project was planned by Fath and Halnes. All modelling and simulations by Halnes. The writing of the paper by Fath.

Paper III: The project was accomplished by Halnes, who acknowledges useful guidance by Åke Brännström at the EEP-program at IIASA. Useful input from Fath and staff at the EEP-program at IIASA.

Paper IV: All authors were involved in planning the project and writing of the paper. Modelling and simulations by Halnes (Model I & II) and Gu (Model III).

Paper V: The project was planned by all authors. Model building and simulations by Halnes. The paper was written by Halnes and Liljenström.

Contents

1 Introduction

Life on earth can be viewed as a myriad of networks nested inside networks. Ecosystems and food webs, at the largest scale, are networks of interacting species. A species is a population of individual organisms that may in themselves be described as networks of cellular and metabolic processes. Cells are, in turn, autonomous structures whose maintenance depends on a network of inner processes, some of which are described by the genetic, metabolic and protein-interaction networks.

All biological systems, from bacteria to large scale ecosystems, are highly complex networks. The parts of these systems interact in such a way that the entire network in some way regulates and organizes itself. Down to the level of chemistry, genes and DNA are believed to have evolved through *self organizing* processes of interaction between their molecular building blocks, forming dissipative structures far from thermal equilibrium (Schneider & Kay 1994). Self organization is a process in which the internal organization of a system, normally an open system, increases in complexity without being managed or guided by an outside source. The idea of networks as self-organizing stems back to Ashby (1957).

While the reductionism tradition in science has tried to understand nature in terms of its building blocks, complex systems often have so called *emergent* properties that cannot be deducted from the properties of their parts alone (see *e.g.,* Aderem 2005). Emergence refers to the way complex patterns arise out of a multiplicity of relatively simple (and often local) interactions, suggesting that the patterns of organization are perhaps more crucial than the characteristics of the building blocks. Self organizing systems typically (though not always) display emergent properties. The function of each part can only be understood contextually, since it depends on the function of all the other parts. Hence, the parts affect the whole (bottom-up effects), as well as the whole affects the parts (top-down effects), and the cause of the systemic properties is then difficult or impossible to define. In the systemic holistic view of life (Capra 1997), there is no strict causal hierarchy between the scales.

The most formalized disciplines of network studies in biology are metabolic networks, protein-protein interaction networks, and gene regulatory networks at the sub-cellular scale; neural networks at the cellular scale, and food webs or ecosystems which are networks of interacting species at the community scale. Between the latter two scales are networks of interacting individuals, such as social insect networks (Fewell 2003), metapopulation models (Hanski 1999), and human social networks which are normally not considered to belong to the realm of biology.

Understanding a natural system implies being able to understand how different aspects of its construction and behaviour are responsible for some large scale functional property of the system. Generally, a network can be studied at four different levels, being that of 1) its structure, 2) its dynamics, 3) its evolution, and 4) its function. Whereas the first three levels deal with *how* the network looks and

behaves, the latter deals with *why* it does so. It is interesting to note that such a concept of a function is not considered in other natural sciences than biology, where for instance the properties of an organ, such as the heart, are often believed to have been selected for because of their beneficial function for the organism as a whole.

The network approach describes a system as a set of units (nodes) and their interactions (links). Some natural systems *look* like networks in the sense that their individual nodes represent physical units (as we perceive them), such as nerve-cells interconnected by nerve fibres in a neural network. Other networks are abstract conceptualizations, such as food webs, where each node represents an entire species or group of species, and the connections are feeding relations (Drossel & McKane 2002). Although the systems in study may differ strongly among each other in their biological reality, they have many features in common at a more abstract level when conceptualized as networks.

This thesis focuses on models of food webs and neural networks. Despite the different biological reality of these two different systems, network modelling provides a framework of concepts and methods that can be applied across system boundaries. Whereas the included papers (Paper I-V) have their own narratives and system specific objectives, they all find themselves under the umbrella of investigating relations between structure, dynamics and function in computational biological network models.

A special emphasis has been put on density-dependent effects, the importance of system complexity, stability-flexibility relations and relations between local and global properties in biological networks. All these concepts have a biological meaning that depends on the system in study. At the same time they are also applicable at a higher level of generality, so that findings within one field may shed light on findings within another.

1.1 Overall objectives

The overall objective of this thesis is to link constructional features (network structure and characteristics of internal mechanisms) of biological networks to their large scale functional properties, and furthermore to investigate the interplay between characteristics at the single node level and the network level.

More specifically it investigates the effect of different aspects of structural complexity on global functions related to the presence and strength of cycles (Paper II), structural stability (Paper I), dynamic stability (Paper III-V) and flexibility (Paper IV-V).

Furthermore, the global functional effects that stem from single node properties are separated from those that stem from the topology of the network (Paper III & V) by increasing the density of interactions in the system from no interactions to strong interactions.

The analyses have been based on computational network models, most of which are novel for this work. A final objective is therefore to provide new methodology that can be applied to related future work.

The more system specific objectives of each paper will be outlined in Section 3 and 4 that focus specifically on food webs and neural networks. In Section 2, these system specific objectives have been projected to a higher level of abstraction where they contribute to an overall understanding of biological networks.

1.2 Outline of the thesis

The thesis is arranged in a modular way. Due to its rather broad scope, the field of biological network modelling will be presented more generally in the following section. In addition, the system specific results from the food web- and neural network studies are lifted to a more general level in the final discussion (Section 5), highlighting important network properties that are shared across discipline boundaries. In between these general sections, the work on food webs and neural networks is presented in two distinct sections that go into more system specific detail on the models and their application within these two separate fields of biological modelling.

2 Biological network modelling

"Somewhere, however, between the specific that has no meaning and that the general that has no content there must be, for each purpose and at each level of abstraction, an optimum degree of generality." (Boulding 1956)

Network theory is an old research topic that stretches back to Euler's solution of the Königsberg bridge problem in the 18th century. Development in computational power and mathematics of complexity has made the field flourish during the last 30 years, and today the network perspective is perhaps the most promising when it comes to describing complex biological systems. In addition to introducing important methodology, an overall aim of this section is to motivate the network approach as a means of understanding living systems, and to demonstrate that biological systems on many different scales have many system properties in common.

Understanding a complex system implies understanding how different aspects of its construction and behaviour are responsible for some large scale functional property of the system. This functional property is commonly discussed in the context of the environment of the system, for instance in terms of how the system responds to an external stimulus.

Network modelling may be regarded as a sub-discipline of system analysis. The network approach very distinctly describes a system as a set of units (nodes) and their interactions (links). At the structural level, network theory coincides with the mathematical discipline of graph theory. The structure of small networks can be analyzed very powerfully by visual investigation of graphs, whereas large networks can look rather "messy". As Newman (2003) puts it, "*the recent development of statistical methods for quantifying large networks is to a large extent an attempt to find something to play the part played by the eye in network analysis of the twentieth century*." The network formalism is especially useful for capturing aspects of the overall organization of large and complex systems. It is particularly useful in this thesis, where the importance of generic structural principles, such as the relation between local and global effects and the density of interactions in biological systems, is investigated.

This thesis does not address the details of any specific system. Nor does it explicitly try to fit models to data in any quantitative way. The applied models are not parameterized with empirical data to such a degree that they could be applied to make quantitative predictions. On the other hand, all the incorporated structural and mechanical principles have a clear biological meaning. The thesis is rooted in making assumptions on underlying principles of organization and interaction in biological networks. The applied models all find themselves at some intermediate level of generality, optimal for this purpose.

This section is structured in a phenomenological way, highlighting general network concepts such as structure, dynamics, evolution and function, rather than on biological system specifics. As they are introduced, these concepts with be given interpretations on what they mean in specific biological networks, especially for the neural networks and food webs that have been the topics of this thesis.

2.1 System boundaries

The first step in any modelling approach is to specify the system boundaries. Checkland (1981) argues that the boundary of a system '*is a distinction made by an observer which marks the difference between ... a system and its environment*'. This generally means that one has to determine which interacting units and which types of interactions one wishes to include in the model. One could speak of external and internal system boundaries. To illustrate the difference between the two, the system boundaries of a food web and a neural network will be briefly defined below.

2.1.1 System boundaries of food webs

An empirical food web is, in its simplest form, a map that specifies who eats whom (links) within a community of species (nodes). The community is normally determined by the species that are believed to play the most important role within a certain habitat, such as a specific bay. The external system boundary is thus partly geographically determined. In addition it is phenomenologically deter-

mined, limiting the study to feeding relations, not considering other kinds of events in the bay. These system boundaries are plausible if the species within the system can be assumed to interact more strongly among each other than they do with species not included in the model. Most food webs are simplified in terms of resolution, lumping similar species into groups (Solow & Beet 1998), so that the network nodes represent functional species (such as trophic species defined as the group of species that share the same predators and prey). Effects due to possible spatial heterogeneity within the community (*e.g.* more shrimps in some parts of the bay than others), behavioural variations between individuals (*e.g.* one cod prefers shrimps while another cod prefers small fish), temporal variations (the cod's diet is seasonal) and so on, are ignored in most large scale food web models. Such limitations of the level of detail included in the model are regarded as internal system boundaries.

2.1.2 System boundaries of neural networks

A neural network is a set of nerve cells interconnected by nerve fibres. The brain processes information by electric signalling across these fibres between millions of neurons. These are the processes addressed by neural network models. The overall activity is related to the mental state of the organism. Of computational (and sometimes also anatomically motivated) reasons, the external system boundaries are restricted to include a relatively small number of neurons. The effect of the remainder of the brain (the environment) is often modelled as a continuous or noisy input to the neural network. The processes through which single neurons generate the electric signalling pulses and the propagation of signals have been modelled at many levels of detail. In this thesis, rather complex neural models are applied, describing how mechanisms in the cell membrane are involved in information processing. Other processes, such as signal propagation, synaptic transmitter release and synaptic plasticity are not modelled explicitly in this thesis.

2.2 Structure of biological networks

The most basic feature of any network is its architecture. In a structural description a network is a map of components and connections that indicate whether two nodes are interacting. Food webs are typically directed graphs, where an arrow from A to B indicates that B preys on A (following the convention that the arrow goes in the direction of the energy flow). In weighted graphs, a weight is assigned to each connection, indicating the strength of the particular interaction. Structural properties of networks can be studied with a high level of generality, since they do not include a quantitative description on the properties of nodes and connections. Box 1 summarises some typical structural graph measures. Network structure is particularly important since it provides the substrate for dynamic processes.

2.2.1 *Structural principles*

A network model typically defines the structure of a biological network, or it specifies some algorithm based on stochastic principles that generate the structure. Canonical examples of structural principles are regularity (meaning that nearest neighbours are more likely to be directly linked) and randomness (randomly interconnected nodes). Most biological systems are not random or regular, but something in between. Box 2 gives a brief review of general graph theoretical studies of biological networks. The more system specific structural features of food webs and neural networks are given in following sections.

Box 1: Structural network measures.

Size (*N*): The number of network nodes.
Link density (*L/N*): The average number of links per node.
Connectance ($C=L/N^2$): The fraction of all possible links that are actually present.
Shortest path: The path that traverses the minimum number of links between two nodes.
Path length (*m*): The number of traversed links in a specific path between two nodes.
Diameter (*D*): The mean shortest path length between all nodes in the network.
Degree (*k*): The number of links that ha specific node has.
Degree distribution (*P(k)*): The probability that a node has k links.
Poisson degree distribution: Randomly connected networks have a sharp Poisson degree distribution. Such distributions are characterized with a modal hump at $<k>$ with exponentially decreasing tails.
Power law degree distribution: The probability that a given node is connected to k other nodes follows a (long tailed) power law $P(k) \sim k^{-\gamma}$.
Long tailed distribution: Any degree distribution that decreases slower than exponentially.
Motif: A small pattern within a network.
Module: A densely connected sub-network within a network.
Small world property: The diameter of the network is small relative to the size *N*. Commonly, networks are termed small if $D \sim log\ (N)$ (Newman 2003).
Connection weights (w_{ij}): The strength of the interaction between two nodes i and j.
Directed graph: Links (arrows) have directions.
Out-degree: In directed graphs: The number of links going out from a node.
In-degree: In directed graphs: The number of links going in to a node.

2.2.2 *Structural complexity in terms of size and connectance*

The complexity of a system is crucial for its function, for instance in terms of flexibility and stability. Structural complexity can be described at many levels of detail. Perhaps the simplest measure of a systems' complexity is the product *NC* of its size and its connectance (see Box 1). This simple definition was used in early stability analysis of randomly connected ecosystem models (May 1972), and has since then been frequently revisited in the debate on the relationship between stability and complexity or diversity of food webs (McCann 2000).

All types of structural features may hide under the global parameters *N* and *C*. The advantage of such a simple measure is that all networks can easily be described in terms of it, so that different network structures may be compared in terms of how their functional properties scale with the complexity *NC*. This measure was useful

as a scaling axis for cyclic structures (Paper II) and stability (Paper III) in different food web models.

Box 2: Structures found in biological networks

Most real networks are somewhere in between random networks and regular networks (such as lattices, where only local connections occur). Even if different biological networks are composed of different nodes and interaction types, they share many features in their structural organization (Jeong et al. 2000; Oltvai & Barabasi 2002; Albert & Barabasi, 2002). In fact, most networks in biology seem to be roughly scale free and follow a power law degree distribution, $P(k) \sim k^{-\gamma}$, where γ is in the range $2 < \gamma < 3$ (Barabasi & Oltvai 2004). Interestingly, this is also true for many non-biological networks such as the internet, electric lines between power plants and co-authorship networks among researchers (Arita 2005; Albert 2005). This suggests that these features may emerge from simple construction rules such as preferential attachment of new nodes (Barabasi & Albert 1999), or from duplication based growth principles (Ravasz et al 2002). A problem with these findings is that most studied networks are in fact samples of larger networks, and do not imply scale-freeness at a larger scale (May, 2006).

The small world property (Watts & Strogatz 1998) denotes that the mean distance between any two nodes (D) is small relative to the size of the system. This seems to be applicable to many biological networks (Cohen & Havlin 2003).The small world effect was early noted in social networks (Milgram, 1967), where it was popularly known as "six degrees of separation". On a still finer level, network studies have revealed substructures within biological networks such as motifs (Milo et al 2002) or modules (Hartwell et al 1999; Ravasz et al 2002; Hintze & Adami 2007). It is acknowledged that all these structural principles at different levels of detail are important for systemic properties such as robustness and adaptation (Albert et al. 2000; Alon 2003; Zhu et al. 2007; Albert 2005; Yook et al. 2004). Detection of modules is also regarded as a means of integrating different functional sub-cellular networks into the cellular whole (Oltvai & Barabasi 2002; Tornow & Mewes 2003).

2.2.3 Weighted connections

From a modelling point of view, including weights to the connections in a graph is a first step towards a more quantitative understanding of its dynamics. Weighted graphs were early used in understanding energy/mass balances (Ulanowics 1972) or cycling (Finn 1976) in food webs. The distribution of connection weights has been found to be highly important for the stability of ecosystems (McCann 2000), something that was investigated further in Paper III. In simple neural network models, weight distribution has been related to associative memories (Hopfield 1982).

2.2.4 Interaction diversity

Another way of increasing model complexity is to allow for different kinds of interactions. A food web is typically restricted to antagonistic relations (–,+) where the prey loses and the predator gains. The more complex ecosystems allow also for other direct relations, such as *e.g.,* mutualism (+,+) and competition (–,–). In cortical networks, the flexibility of the neurodynamics is dependent on a fine balance between excitatory (one neuron increases the activity of another) and inhibitory interactions (one neuron decreases the activity of another).

2.3 Dynamics of biological networks

In dynamic network models, each node will have a state value that varies over time due to interactions with other nodes. For instance, in a food web the state value of a node typically represents the population of a species. The state of a neuron is usually its cross membrane potential.

In early studies, Boolean state values, where nodes are either "on" or "off", have been used as simplistic first approaches to model gene networks (Kauffman 1969) and neural networks (McCulloch & Pitt 1943). Later models operate with continuous node models for potential variations in neural membranes or for the accumulation of gene products (see *e.g.*, Hopfield 1984; Vohradsky 2001).

The connections between nodes are generally described by differential equations that determine how the state value in one node is affected by the state values in other nodes. In food webs the state variables (populations) vary due to feeding relations. In neural networks, the cross membrane potential of a neuron varies due to inputs/outputs from/to interconnected neurons in the network.

Due to different characteristics of the interactions, some of the generality of the structural network analysis is lost when network dynamics is studied. Yet, also many dynamical principles are shared between different networks. A fairly simple equation from neural network modelling (Hopfield 1984) will be discussed in a general way to illustrate some general concepts for network dynamics:

$$\frac{du_i}{dt} = \sum_{j \neq i} w_{ij} g_j \left[u_j(t) \right] - \frac{u_i}{\tau_i} + I_i(t) \,. \tag{1}$$

Equation (1) determines how the state u_i (i.e. the cross-membrane potential of a neuron or the mean membrane potential of a group of neurons) of a node varies in time. If the node is left in isolation, u_i will decay due to the second term on the right. Inputs to node i at each time unit are the input from outside the system ($I_i(t)$) and the sum of inputs from other nodes. Some function g_j relates the state of node j with its output to other nodes, while the connection weights (w_{ij}) determine the strength of the specific connection between the nodes i and j (i.e. how much the output of j affects i). Formally, unconnected nodes have w_{ij}=0.

The functional form and the interpretation of the interactions will depend strongly on the model system. However, it is common in biological network models to do as described above and assume that all interactions have the same functional form (or at least to limit the system to a small number of different interaction types). In this way only the linear connection weights determine the differences in interaction strength across the system. It makes sense to assume that, for instance, all feeding relations in a food web or signalling processes in neural networks have the same form, and vary only in strength. The set of weighs w_{ij} is a weighted graph that contains all the information about the structure and the internal differences between connection strengths. In neural networks the connection weights are

analogous to the strength of the synapses. In food webs they interpret as a predator's predation efficiency on its prey.

In most cases of dynamical network analysis, the set of differential equations is too complex to be solved analytically. Hence, numerical methods must be applied. Technically, this means that some initial values for all parameters and state values must be specified at a particular time t. The right hand side of the equation can then be calculated, giving the increase/decrease du_i/dt at the particular time t. Then this initial increase/decrease is calculated for all nodes i and added to the state values, so that for the next time step $t+\Delta t$ (if using the Euler method):

$$u_i(t+\Delta t) = u_i(t) + \frac{du_i(t)}{dt}\Delta t \ . \qquad (2)$$

This procedure is repeated for time step after time step to find a numerical value for the state values for all the discrete time steps.

In general there are three options for the time development of a complex system. After a certain time called the transient period, the dynamics of the system will either reach 1) a point attractor, 2) a cyclic attractor, or 3) a chaotic attractor (see Box 3). The dynamic equations and the connection weights decide the different attractors that a complex system has. In neural models, the set of weights are updated through learning processes (Hebb 1949; Hopfield 1982; Kohonen 1988). Associative memories may be stored in a distributed manner in the system as attractor states determined by the set of weights (w_{ij}).

Box 3: Dynamic attractors (see *e.g.*, Strogatz 2000)

1) Point attractor: A static equilibrium where all state values end up at fixed values that do not vary over time. The criterion of neighbourhood stability in food webs demands that a stable system remains at a point attractor so that all populations remain constant over time.

2) Cyclic attractor: The situation where state values oscillate so that the network has a repeated activity pattern. Cyclic attractors have for instance been found in simple two-species predator-prey systems described by Lotka-Volterra equations (see *e.g.*, Gotelli 1991).

3) Strange attractor: A chaotic and unpredictable activity pattern that still has some ordered features, and that is locked into a certain region of phase space. Cortical neurodynamics exhibit stationary chaotic activity when a test-person is involved in a specific cognitive task.

2.3.1 Node complexity

The differential equations that specify the intrinsic activity of single nodes and their response to other nodes is the mathematical fundament for the network dynamics. The term *node complexity* will be used to describe the functional complexity of these equations. The level of biological detail (internal system boundaries) should be carefully suited to the problem one wishes to model. For instance, in Paper V regulatory processes of ion-channels at the single neuron level are stud-

ied. The neural model in this paper is more complex than the model in Paper IV, where these detailed processes were not the subject of study.

2.3.2 Node diversity

The complexity of a network can be increased by allowing different nodes to respond differently to the same input, in terms of their intrinsic mechanisms. In Paper V, diversity was implemented by altering parameters in the intrinsic equations for a subset of the nodes. Note that variations in the connection weights are covered by the terms *structural complexity* and *interaction diversity*, and are not considered as *node diversity*.

2.3.3 Network density

The effect of network density is a major topic in this thesis. *Network density* is defined simply as a measure of how strongly the units affect each other, in terms of a mean (or mean squared) connection strength, taken over all connections. Network density is not related to the unweighted structure of the network (such as link density which is related to the number of links). The term *density* is chosen to propose a relationship between the spatial density of nodes in the network and how much they interact, as will be justified below for food webs and neural networks. The purpose of introducing such a term is to discuss in parallel how the network density will affect the stability and flexibility of neural networks, and the stability of food webs (see Section 5).

The first model of predator prey-dynamics was the famous Lotka-Volterra (LV) model for two species (see *e.g.*, Gotelli 2001). If P is the predator population and H is the prey population, the LV-equation for the prey's population dynamics may be written as:

$$\frac{dH}{dt} = r(1 - H/K)H - aHP \tag{3}$$

In the absence of the predator, the density dependent logistic term $r(1-H/K)H$ will stabilize the population at the carrying capacity K, limiting the possible population that can live in a certain habitat. The population decline due to predations on P by H, is assumed to be proportional to the encounter frequency which scales like HP, with the proportionality constant a (which is somehow related to the efficiency of the predator in this particular relation). It seems likely that in a dense community, the encounter rate should increase. Hence, a denser system could be assumed to be characterized by higher values of the proportionality constants a. A similar relation between a and the density has been applied in food web models with adaptive foraging, where each specific interaction is assumed to depend on the densities of all species in the community (Jordan & Scheuring 2004).

Similar density relations can be found in the human brain. At least at a large scale, interconnectedness is known to be highly dependent on spatial distances, and neu-

rons belonging to neural assemblies that are active in the same functional task are likely to be closely located and characterized by strong interconnections. Of computational reasons, the models in Paper IV-V are restricted to relatively small networks on spatial scales where distant dependent connectivity might be negligible. They are, however, regarded as first approximations to model neurodynamics at a large scale, and distance dependent connection weights are therefore assumed. Hence, also in neural networks, the average interaction strength may be regarded as a density effect.

Density effects are found also at the nodal scale, such as the carrying capacity of a population in a food web, or the density of ion channels in neural cell membrane.

2.3.4 Relationship between scales

Another main topic of this thesis is the relationship between properties at the single node scale and at the network scale. If all interactions (and accordingly, the network density) were zero, the network activity would depend entirely on the sum of the isolated node activities. Hence, increasing the network density is a way of bringing the nodes closer together. In this way the relationship between intrinsic node properties and properties that emerge globally from interactions at the network level can be investigated. Paper V demonstrates how the relationship between network density and the density of ion channels at the cellular level is crucial for the large scale dynamics of a neural network. The results of Paper III for food webs are discussed in a similar context in the final discussion (Section 5.2).

2.4 Biological network evolution

Network evolution occurs when the network structure changes over time. This happens when nodes and connections between nodes are formed or disappear, and/or when the connection weights develop over time. In certain food web models, network evolution is directly linked to Darwinian evolution in the sense that the disappearance of a node represents a species going extinct, and the formation of a new node represents a new mutant or invader entering the food web (Drossel & McKane 2002). In models where both network dynamics and network evolution are considered, the latter is usually assumed to happen at a much slower time scale.

The structures of neural networks evolve during the lifetime of the organism in processes connected to learning and adaptation. The main paradigm of learning relates to synaptic plasticity, and refers to the process where neural networks adapt or store memories by updating the synaptic strength (Hebb 1949; Baudry 1998). Technically, this is equivalent to updating the connection weights.

Although different structural properties have been applied in different simulations, processes of network evolution are not explicitly modelled in this thesis. Instead, the objective of this thesis is to relate some large scale properties of biological

networks *as they are* to their construction in terms of their structure and dynamic characteristics.

2.5 Function of biological networks

To be useful, a network approach to biological systems should take function into account. It is a rather ambiguous term, but the most general function of a biological system is to generate some action that makes it survive and adapt properly to environmental events and changes at several time scales. The function could for instance be to make the system efficient in terms of energy, time and accuracy, or to make it stable or flexible according to some measures. A brief commentary on network evolution and function is made in Box 4. Interestingly, a certain degree of disorder (randomness/stochasticity) often seems optimal for many biological systems and processes (Wiesenfeld & Moss 1995; Århem et al. 2000; Strogatz 2001; Liljenström & Halnes 2004).

Box 4: Evolution and function

It seems natural to assume that biological network features have been selected for because they serve a certain function. However, natural selection act at the individual level and it is a matter of debate to which degree selection processes can shape overall structural network features (Wagner 2003). Also, biological networks share structural scaling principles with pre-biological chemical reaction networks, suggesting that certain features of biological network may have been moulded by other processes than natural selection (Wagner 2003). Graph-theoretical studies explain how global scaling properties of biological networks may be explained by the logic of preferential attachment of new nodes (Barabasi & Albert 1999), or by duplication based growth principles (Ravasz et al 2002). Other studies focus on thermodynamic principles and constraints (Schneider & Kay 1994; Jørgensen & Fath 2004). However, the different explanations of network features are not mutually exclusive, and the observed network features may be a matter of which process provides the strongest constraint.

The general function of the brain is intuitively understood: It intuitively understands its own function, it makes decisions, it produces a visual subjective image of the external world based on sensory input from the eyes, it recognizes the face of a friend in a fraction of a second and learns how long an egg is supposed to boil. Sometimes it even forgets things.

The general function of a food web or an ecosystem is less clear. This is due to the fact that these systems are living systems studied at the largest scale. The spikes of a hedgehog, for instance, have the function of protection against enemies within a given environment. An ecosystem has no such obvious environmental challenges to react upon, at least not if the systemic interactions are described in terms of annual averages, comprising seasonal variations. From an anthropocentric point of view, one could speak of *ecosystem-services*, suggesting that the function of an ecosystem is to provide human beings with resources and nice places to spend holidays (eco-tourism). Although a functional concept like this is not useful for explaining the structure and dynamics of an ecosystem from an evolutionary perspective, it makes sense in a management context.

In the network perspective, function is normally discussed in terms of some global system property, which is believed to depend on certain constructional features of the network (Newman 2003; Liljenström & Halnes 2004). In general, it should be essential that the system is stable to short-term fluctuations and common insignificant events. At the same time it should also be flexible so that it can react to weak signals and rare important events, as well as adapt to long-term changes. The stability and flexibility, as well as the efficiency of a biological system is dependent on such parameters as the structure complexity, rate constants and the amount of energy invested in constituents and dissipated in the system. In general terms, stability is often defined in terms of a system's ability to remain at attractor states, and flexibility as the ability to switch between attractor states in a consistent way (Kitano 2004; Ashwin & Timme 2005).

The aim of this thesis is to relate certain structural and dynamical features of networks to their function within a larger context. The function of a neural network could for instance be pattern recognition, associative memory or classification. As mentioned before, neural learning and adaptation are associated to processes of network evolution and the mechanisms behind them. The short term state of the brain, which is the main focus in this thesis, is related to the real-time dynamic signalling in the brain. When a test person solves specific cognitive tasks, the activity is correlated to certain features of the global dynamics of a brain region (see *e.g.*, Fingelkurts & Fingelkurts 2006). At the short time scale, brain function is therefore directly related to large scale neurodynamics. The dynamics should be stable in the sense that it should remain stationary when working on the same task, and flexible in the sense that it should be able to jump between states when something forces the test person to undertake new and different mental tasks.

Thermodynamic-based goal functions (Fath et al. 2001) suggest that ecosystems develop to maximize dissipation (Schneider & Kay 1994), energy throughflow and energy storage (Fath et al. 2004). Still, the perhaps most important functional concepts in the ecosystem/food web literature deal with robustness and stability (McCann 2000). Food webs are believed to look like they do because they are stable. It seems likely that ecosystems should be robust to external variatons (such as climate fluctuations, seasonal variations, species invasions and mutations) and have stable intrinsic dynamics. Functional stability is also a useful concept in management issues, dealing with sustainability and minimizing the effects of human impacts. It is a task for science to define appropriate stability measures, and to relate these to the structure and dynamics of ecosystems.

Some of the functional properties that have been studied in this thesis will now be briefly introduced. Their meaning and definitions at a detailed level are highly system specific, and will be discussed more thoroughly in the sections on food webs and neural networks.

2.5.1 *Structural robustness*

The structure of a biological network is the substrate for its dynamics. Structural changes happen at a longer time scale than dynamics, and are more critical. It is crucial that important aspects of the structure are robust to (relatively) small structural changes. For instance, it should be essential that a network is not easily split into two separate sub-networks by the removal of a single link or node. A network is structurally robust if important structural aspects are not severely affected by the removal of a single node or link.

2.5.2 *Structural cyclicity*

Structural cyclicity (Jain & Krishna 2003) is a structural feature of a network. Cyclic structures are important for matter/energy recycling and feedback effects. Two nodes sitting in the same structural cycle in a directed graph can in principle interact indirectly along an infinite number of pathways of different length corresponding to any number of orbits around the cycle. The structural cyclicity of a network is correspondingly a measure of how fast the number of indirect pathways of a given length m increases with m. The relationship between nutrient cycling and stability also has been a recurrent theme in the ecological literature (DeAngelis et al. 1990).

2.5.3 *Dynamic stability*

In dynamic systems, state values fluctuate over time. Eventually this may result in structural changes, such as species extinctions in food webs (meaning that the state value drops to zero and a node disappears). Dynamic stability may be defined in many ways. A food web may be defined as dynamically stable if its dynamics guarantees that no species go extinct. A stricter criterion, called neighbourhood stability, demands that all populations are stable at a fixed point attractor.

At a more general level, stability requires that the system dynamics remains stationary in some aspect. For instance, the global neurodynamics of a sleeping person should show a persistent slow wave oscillation that is robust to insignificant disturbances (ensuring stable sleep). Stationary brain-dynamics correspond to either cyclic or chaotic attractors (see Box 3).

2.5.4 *Dynamic flexibility*

The function of cortical networks is directly linked to the interplay between stability and flexibility in the large scale neurodynamics. If the fire alarm goes off, the sleeping person in the previous example should preferably no longer experience stability in his or her cortical dynamics. The dynamic should rather switch to some other, high frequency and alert state, characterized by a different attractor. This ability to switch between states is defined as the flexibility of a neural network. It may be triggered by external inputs, as in the example above, or by internal mechanisms or intrinsic dynamic properties.

2.6 General overview of papers

The papers included in this thesis are arranged as a journey into the complexity of biological network models. The starting point is qualitative structural descriptions of biological networks, and the level of detail in the dynamical description of node properties is then gradually increased. Along this journey, new features, both structural and dynamical, are revealed as crucial for the function of biological networks. The functional properties considered are all related to stability and flexibility. A schematic overview of the papers included in this thesis is found in Figure 1.

The analysis begins at the purely structural level, with an application to food webs as these are often studied as directed graphs (weighted or unweighted). The structural functional measures are structural robustness and structural cyclicity. Paper I and II show how these functional properties depend on the architecture of food webs, with a special emphasis on pathways due to decomposing and recycling of dead organic matter. Five food web models are compared, one of which is novel for this work. Certain aspects of the network architecture are found to be highly important for the structural robustness (Paper I) and structural cyclicity (Paper II) in food webs.

Dynamic analysis addresses more quantitative aspects of biological networks. Not only the architecture, but also the distribution of interaction strengths and intrinsic properties of the nodes are important. System dynamics is implicit in the weighted graphs in Paper III, introducing the requirement of a stable fixed point (Box 3) as the first dynamic functional measure of this thesis. Dynamic stability depends not only on the network architecture, but also on the strength and characteristics (*e.g.*, antagonistic, mutual or competitive) of interactions. Paper III shows that the stability of food webs depend strongly on their architecture and distribution of interaction strengths, especially in networks of intermediate network density.

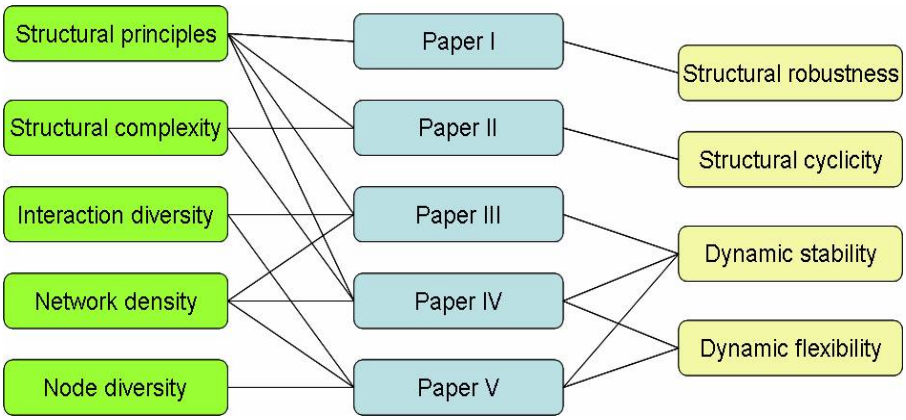

Figure 1: An overview of the papers included in this thesis.

Network dynamics is studied more explicitly in Paper IV & V, with application on neural networks. The dynamic functional measures are the stability and flexibility of their large scale dynamics (mean activity taken over all nodes). The networks are described by differential equations that include a high level of biological realism in the description of single node mechanisms. This detailed dynamical description reveals that network function depends not only on architecture and link distribution, but also on a fine balance between inhibitory and excitatory mechanisms (Paper IV), between local and global interactions (Paper IV), and between properties at the single node scale (density of ion channels) and network scale (network density) (Paper V).

All the modelling setups and simulations presented in this thesis follow the same logic: I) First, the network model is constructed, specifying external system boundaries and internal structure and mechanisms. The model contains a set of parameters that determine the network structure and the characteristics of the dynamical interactions. II) Secondly, some functional measure is specified and identified as a network property that emerges from these underlying constructional characteristics specified by the set of parameters. III) Thirdly, simulations are run. The model parameters are varied from simulation to simulation in order to see the effect that these variations have on the function of the model.

3 Food webs and ecosystems

"Most of what is interesting about biological communities cannot be pinned, stuffed, pressed onto herbarium sheets or preserved in alcohol" (Thompson 1982).

Single-species approaches to management are based on 19th century reductionism, assuming that the dynamics of species can be viewed outside of their role in the ecosystem. The ecosystem or food web based approach to management starts at the other end of the scale by recognizing the complexity and holism of the system (Fath et al. 2007). A food web is in its simplest form a network where the nodes represent species (or groups of species) and the directed connections represent feeding relations. An example of a food web can be found in Figure 2. Even such a qualitative description summarizes a great deal of information on diversity, species composition, trophic structure, chain length and species interactions (Pimm et al. 1991; Williams & Martinez 2000).

These large scale systems are commonly studied at correspondingly large time scales. At the *evolutionary time* scale, it may be expected that significant changes in community structure and genetic make-up will occur. This thesis focuses on the *ecological time* scale (of the order of tens of generations). At this time scale the population interactions are assumed to lose their explicit dependence on spatial distribution, since spatial heterogeneity in the species distributions within a habitat is assumed to even out (Ulanowicz 1972).

It should be noted that these assumptions and simplifications are a matter of study -focus. High resolution studies exist for smaller subparts of ecosystems, addressing spatial issues such as habitat fragmentation and demographic stochasticity (see e.g. Polis & Hurd 1995; Casagrandi & Gatto 1999).

A food web is a sub-network of an ecosystem, which generally refers to a broader picture, including a higher diversity of interactions, such as mutualism, competition and predator-prey relations. Only predator-prey interactions are studied in food webs (Drossel & McKane 2002). The convention that the arrows go from the prey to the predator is used throughout this thesis, indicating the direction of the energy flow. Ecosystems require a more abstract description linking population dynamics in two connected nodes. Model food webs and ecosystems are still often used in similar studies, and findings from the two fields are not always kept apart. The difference between them in terms of stability is investigated in Paper III.

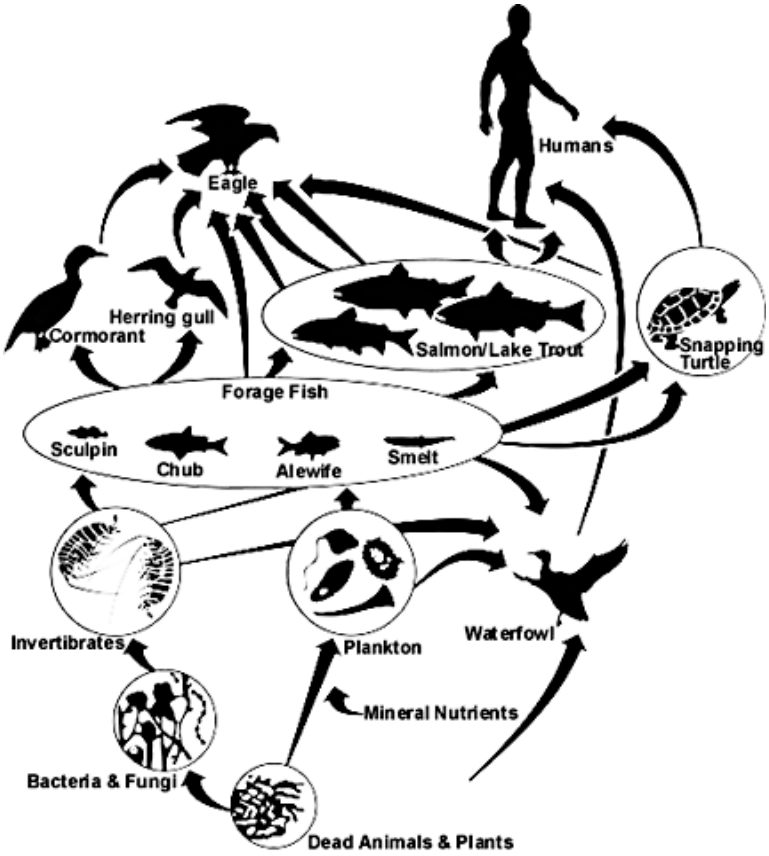

Figure 2: Example of a food web, illustrating functional grouping. (The picture was taken from http://www.mindfully.org/Food/Food-Web-Simply.htm.)

The interplay between different interactions is difficult to parameterize, and quantitative ecosystem studies are often limited to a small number of species, whereas

the food web models allow for larger communities to be treated. Still, even food webs cannot include all species in the habitat, so the nodes will in most cases rather represent a class of "similar" species, such as for instance trophic species, defined as a group of species that share the same predators and/or preys (Pimm et al. 1991).

Empirical food web studies aim at identifying their most important structural features and describing them at a level of detail which is sufficient to explain their most essential functional characteristics. However, methods of sampling food web data have been inconsistent. The role of mammalian predators which look "sexy" to the human eye may historically have been overestimated, while less conspicuous species, such as spiders, are more easily lumped into one functional group (May 1999). Many food web properties will depend on how "similar" species are aggregated into trophic species (Hall & Rafaelli 1991; Drossel & McKane 2002). Several empirical food webs could easily be reduced by species aggregation (Solow & Beet 1998). In this way, the number of species will depend severely on judgments made by empiricists. Systematic species aggregation in empirical webs is now commonly used as a means of reducing methodological biases (Williams & Martinez 2000). Another and more practical problem is that links may vary over time. For instance, a predator may have a seasonal preferences for different prey, so that data gathered over longer periods may contain more links than are actually present in the system at any fixed point in time (Drossel & McKane 2002).

In addition, some food webs include one or several compartments for detritus (dead organic material). However, there is no consistent approach for incorporating them, something that shows the difficulties in defining clear system boundaries (Drossel & McKane 2002). Detritus alters generalizations of the structure and function of food webs (Moore et al. 2004), but has been overlooked in many studies. Paper I and II show that the detritus compartment is of great importance for a complete food web picture, altering structural robustness and cyclicity.

3.1 Food web objectives

The objectives for the food web studies are listed below.

- To develop a simple structural food web model that takes the effect of decomposing of dead organic material (detritus) in food webs into account (Paper I), and to study the effect of decomposing detritus on food web robustness (Paper I) and global energy cycling (Paper II).

- To compare different food web models in terms of their robustness (Paper I), global energy cycling (Paper II) and dynamic stability (Paper III), and to investigate how these properties scale with the complexity of the food web.

- To detect structural differences between stable and unstable food webs (Paper III).

- To compare the stability of food webs (containing only antagonistic predator-prey relations) with the stability of ecosystems (containing antagonistic, mutualistic and competitive interactions) in a simple model (Paper III).

3.2 Management applications

Habitat loss due to landscape fragmentation following agriculture, building of roads, river dams and other kind of land exploitation are today assumed to be the most important threat towards biodiversity. The loss of habitat area is often accompanied by the disappearance of species, especially in the upper trophic levels of food webs. Recent predictions show that habitat area alone is not sufficient to predict changes in population sizes, but that also food web structures in small versus large habitat fragments are crucial for controlling abundances of multiple species (Kruess & Tscharnkte 2000; Gotelli & Ellison 2006). In addition, global warming has altered life conditions for many species, and recent food web studies address environmental feedback mechanisms related to for instance temperature (Bagdassarian et al. 2007) or CO_2 (Legendre & Rivkin 2002).

Simple food web models, used either as core or component hypotheses, provide a systematic and enlightening way to grasp a complex system as a whole. Structural and dynamic food web models can organize our thinking about a range of applied problems, such as detecting important structural features and evaluating mechanisms that control populations. Food web models may also be incorporated as one element in models of regional mass balances (Power 2001), or in integrated socio-ecological models (Tallis & Kareiva 2006).

Due to the relatively low resolution of food web models, specific quantitative predictions will in most cases be unreliable. Yet, if used with healthy scepticism and in combination with knowledge of local natural history, food web models can promote the iterative feedback between prediction, falsification by observation, and new prediction (Power 2001). Understanding relationships between structure and functional properties of food webs and ecosystems is of high relevance for ecological management. The models of Paper I-III provide methods for detecting, in general and abstract models, which features and links in a food web are important for its global function. The results are qualitative, yet they identify features that are likely to play the most critical role for system function, and can guide managers and policy makers on where the main efforts and caution should be focused.

3.3 Food web structures

Many features in food webs that were earlier believed to be roughly scale free (Pimm et al. 1991), have later been found not to be so. A more recent analysis (Dunne et al 2002) suggest that the disagreements on food-web structures are based on selective use of relatively few sampled food webs. A scaling relation (for some parameters γ and ξ)

$$P(k) = k^{-\gamma} e^{-\frac{k}{\xi}}, \quad (4)$$

was recently proposed for the link distribution of food webs (Montoya et al 2006). The last factor on the right decreases the probability of a species having a high number of links, especially in large food webs. Such a modified power law may explain the discrepancies between the scaling of early, smaller food webs and more recent larger food webs.

This being said, much is still known about the structure of food webs. Even if they formally might not be scale free or small worlds (see Box 1), they are characterized by a long tailed degree distribution and are densely interlinked (Ulanowicz & Wolff 1991; Williams et al 2002). Furthermore, they have a bias towards hierarchical chain-like interactions (Cohen & Newman 1985; Milo et al. 2002; Garlaschelli et al. 2003). To some degree, feeding relations can be correlated to species' body-mass (Cohen et al 1993). They seem to be characterized by a distribution of weak vs. strong links (Ulanowicz & Wolff 1991, McCann 2000; Neutel et al. 2002) that is favourable for their stability. This is further investigated in Paper III.

Cyclic structures were early identified in food webs (Lindeman, 1942), but have commonly been neglected in food web models, partly, it seems, due to the lack of analytical tools. However, the presence of cycles has been emphasized in many studies as one of the most important features of ecosystems (see *e.g.*, Ulanowics 1983; Patten 1985; Burns 1989). Cycles affect the residence time of nutrients, act as stabilizing buffers for fluctuations in energy supply, and generally affect ecosystem functioning (Allesina & Ulanowics 2004). A technical argument for their importance is that cyclic structures will significantly increase the number of higher order pathways between two nodes (Borrett et al 2007). Even if each path carries a small amount of energy, the high number of different higher order pathways will add up to give an important contribution (Lenzen 2007).

3.4 Stability of food webs

The idea that there is an important connection between stability and diversity/complexity has been subject to many debates (May 1972; Lawlor 1980; McCann 2000; Kaiser 2000). As for other biological networks, food webs are found to be rather robust with respect to random removal of nodes (Sole & Montoya 2001). They are more fragile to specific attacks at keystone species, although their relatively high connectance makes them more robust to removal of highly connected nodes compared to many other biological networks (Dunne et al 2004). Paper I investigates the effect that a detritus compartment has on the structural robustness of simple food web models.

For decades leading up to the 1970s, the dominant ecological paradigm was that complex systems were more stable than simple ones (Odum 1953). This was

seemingly accepted as a rule of thumb until May used dynamic mathematical modelling in random networks to arrive at the opposite conclusion (May 1972). May showed that in terms of a linear stability measure, complex networks tend to be less stable than simple ones. May's findings started a more quantitatively based stability-diversity debate.

There are three main objections to May's conclusions. I) First, real food webs/ecosystems are not randomly connected (De Angelis 1975). Real ecosystems have been found to be more stable than random networks, even when using May's stability criteria (de Ruiter et al. 1998). II) Secondly, the stability of a food web will also be strongly dependent on the level of detail (realism) in the dynamic model equations (Polis 1998; Pelletier 2000). More recent modelling approaches have shown that food webs including adaptive foraging may yield a positive relationship between complexity and stability (Kondoh 2003), although it has been pointed out that such a positive relationship is highly model specific (Brose et al. 2003). III) Thirdly, the criterion of neighbourhood stability might not be the most relevant stability measure since a model ecosystem might very well be regarded as stable even if it has no fixed point equilibrium. For instance, it may have other attractor states that ensure that no species go extinct, and many other stability measures have been proposed in the literature (Lawlor 1980; Law & Morton 1996; McCann 2000). To mention a few, *permanence* (Law & Morton 1996) defines a system as stable if it guarantees that no species go extinct. *Resilience* is used with several specific meanings, but is loosely defined as a measure of how well the system is able to maintain its function when faced with a novel disturbances (Holling 1973; Webb 2007).

Different measures of stability are not mutually exclusive and should be regarded as complementary in understanding the dynamics of food webs. Paper III revisits May's criterion of neighbourhood stability. The simplicity of the approach provides a good framework for studying the importance of food web structure and link distribution for system function. The work exceeds May's original work by considering realistic food web structures and the importance of the distribution of interaction strengths.

3.5 Food web models

Food webs are subject to evolution. Many models have been developed to suggest how, most of which belong to one of two different groups. Assembly models (Post & Pimm 1983; Hang-Kwang & Pimm 1993; Law & Morton 1996; Fukami 2004) let food webs evolve through series of invasions (from an outside species pool) and extinctions (determined by intrinsic system dynamics). Evolutionary models (Caldarelli et al. 1998; Drossel et al. 2001; McKane 2004; Loeuille & Loreau 2005) let food webs evolve from series of mutations (of internal species) and extinctions. The end product of all these models is usually a food web that is resistant towards invasion and mutation effects, and dynamically stable within itself. These models are also able to explain certain structural aspects of empirical food webs, as emergent from the evolutionary process and the constraint of stability.

This thesis focuses on a different class of food web models that try to capture important structural aspects of food webs as they are today, not considering evolutionary processes (Cohen & Newman 1985; Martinez 1992; Williams & Martinez 2000; Fath 2004). These models incorporate simple principles of how food webs are interconnected into algorithms (Box 5), so that they can produce a great variety of food webs based on these principles (see Figure 3 for illustrations). The motivation is partly to complement the rather sparse amount of empirical food web data with "realistic" model food webs, and partly to see if the assumed construction principles are feasible in the sense that they reproduce empirically observed food web features. The models are also easy to manipulate in terms of network size (N) and connectance (C), so that they can be used to see how certain network properties scale with these parameters, and in such a way establish relations between structural principles and network function. This thesis compares all these models in order to relate structural principles to global functions such as structural robustness (Paper I), energy cycling (Paper II) and dynamic stability (Paper III) in food webs.

Box 5: Structural food web models

Constant connectance model (Martinez, 1992): N species are connected randomly among each other. All connections have the same probability C of occurring.

Cascade model (Cohen & Newman 1985): N species are ranked by number from 1 to N. All connections go upwards in the hierarchy, and occur with the same probability $2C$.

Niche model (Williams & Martinez 2000): A niche value ($0 < n < 1$) is randomly assigned to each species. Species' predate within a range r of niche values ($r = x*n$, where x is a random number drawn from a beta-distribution with expected value $2C$). The centre of the predation interval is drawn from a uniform distribution on the interval $[r/2, n]$.

Modified Niche model (Paper I): A food web with $N–1$ species is generated by the original niche model. A detritus compartment is added (species N). All species contribute (arrows in) to the detritus compartment. Species feed on detritus with probability C.

Cyber ecosystem model (Fath, 2004): N species divided into six functional groups (detritus, detritus feeders, primary producers, herbivores, carnivores and omnivores), which determine possible and not possible feeding relationships. The model is tuned to have only N and C as input parameters by using a fixed distribution of N species, using one detritus compartment, one compartment for detrital feeders, and $N–2$ species evenly distributed in the remaining four groups.

The earliest models were different versions of random models (May 1972; Martinez 1992), where all N species are connected randomly among each other. The counterpart to the random models was the strictly hierarchical cascade model (Cohen & Newman 1985), whose structure is a set of food chains originating in basal species (in-degree equal to zero) and terminating at top predators (out degree equal to zero) (see Box 1). Real food webs are definitely not randomly connected. Nor are they strictly hierarchical. A later assembly model is called the niche model (Williams & Martinez 2000) and has become one of the most accepted models. As in the cascade model, the species are hierarchically ranked. A niche value (be-

tween 0 and 1) is randomly assigned to each species, and predators are then allowed to prey on a niche interval centred below their own niche value with possible overlapping (see the intervals in Figure 3C). The niche overlap allows some predations to exert downward in the niche hierarchy, and opens the possibility for structural cycles. The niche model has been tested against both random and cascade models (Dunne et al. 2002; Martinez et al. 2006), and has been proven more successful in reproducing several empirically found food web properties. The niche values and predation intervals can to some degree be correlated to body size dependent predation tendencies since the most common situation is that a predator predates on an interval of species that have a similar, but in 90% of the cases, lower body mass than itself (Cohen et al. 1993).

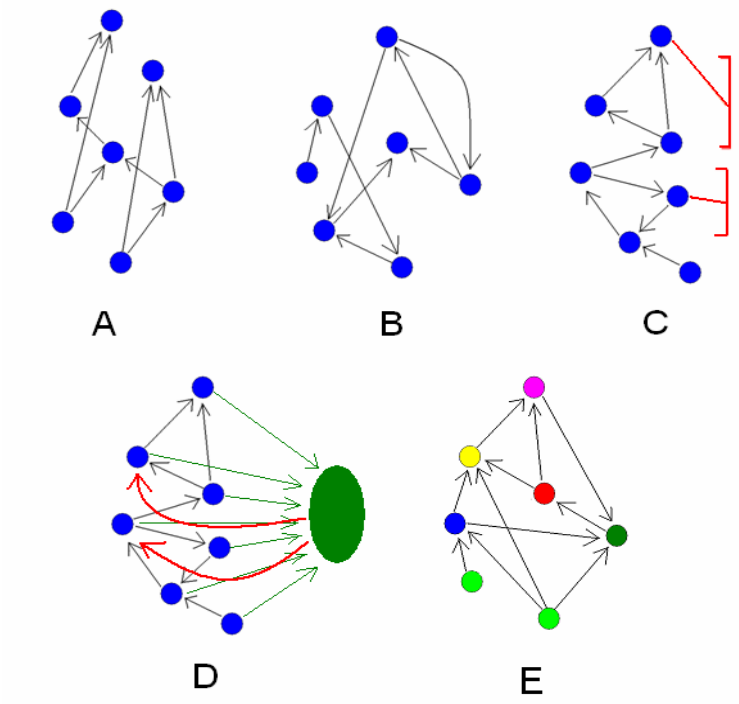

Figure 3: Model food webs: **A**) Cascade model, **B**) Random model, **C**) Niche model, **D**) Modified niche model (the large compartment to the right is the detritus compartment) and **E**) The cyber ecosystem model.

None of the models described above recognizes the additional pathways due to decomposing and uptake of dead organic material (detritus). The detrital pathways (via a detritus compartment) are likely to be structurally different from the conventional predation links in the system. The cyber ecosystem model (Fath 2004) is slightly more complex than the other models. Instead of just the total number of compartments (N), it operates with six functionally different categories (primary producers, grazers, omnivores, carnivores, detrital feeders and detritus) that connect to each other in accordance to ecologically realistic rules.

This thesis contributes to the theory by proposing a simpler model for including the detritus compartment (Paper I) in order to specifically study the effect of decomposing and recycling of dead organic material. The model is called the *modified niche model*, and technically modifies the original niche model by including a detritus compartment and connecting it in a realistic way to the species in the original food web. As part of the modified niche algorithm, the detritus compartment connects differently within the system than the conventional predation links between the species (see Figure 3D). The modified niche model enters the line of simple food web models that only take N and C as input parameters. In addition, a third parameter a (see Section 3.9), related to the network density (mean interaction strength), is introduced in Paper III, where the structural food webs are described as weighted graphs in order to study dynamic stability.

It should be noted that the structural food web models considered in this thesis are very general, and the nodes are not taken to represent specific species. This means, in principle, that any of the nodes in any of these models could be said to represent a detritus compartment. The reason for adding it explicitly is the argument that this compartment is connected differently within the system than the conventional predations. The modified niche model (Paper I) assumes that all species contribute to the detritus pool, and that some species may feed on it, thus creating feedback loops from the top predator to some lower level in the system.

3.6 Simulations with food web models

All the work on food web modelling presented in this thesis follows the same logic, described by the following four steps: 1) Food web models (presented in Box 5) were programmed in Matlab so that they could produce a variety of food web structures based merely on a few input parameters (N, C, a) concerning the structural complexity (see Box 1) and mean interaction strength. 2) Parameter values (N, C, a) were specified. 3) Some functional measure (structural robustness, structural cyclicity, dynamic stability) was defined. 4) Simulations were run for different models and different choices of model parameters (representing structural characteristics of the webs), in order to investigate the effect of structural principles and parameters on the function of the food webs.

$$C = L / N^2 , \tag{5}$$

was used as a definition for the connectance, where L is the total number of links in the network, and N^2 is the theoretical number of possible links. Although cannibalism (self-links) is often excluded in these models, N^2 (as opposed to $N(N–1)$) is still used in the formal definition of C. The mean interaction strength a is defined in Section 3.9.

When any of the food web models in Box 5 are run, they produce a food web structure that is represented by an $N \times N$ adjacency matrix of binary elements (a_{ij}) that indicate whether species i feeds on species j ($a_{ij} = 1$) or not ($a_{ij} = 0$), as illus-

trated in Figure 4. The aim of these models is to reproduce realistic food web structures. The model food webs are compared to empirical data sets in Figure 5.

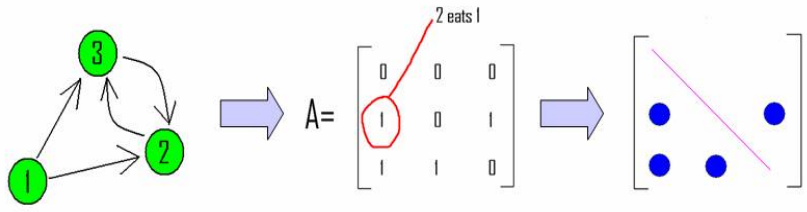

Figure 4: Simplistic sketch on how a food web graph translates into an adjacent matrix. The spy plot (to the right) presents only the links (1's) in the matrix and is of value for visual investigation. Downward arrows will result in matrix elements above the main diagonal.

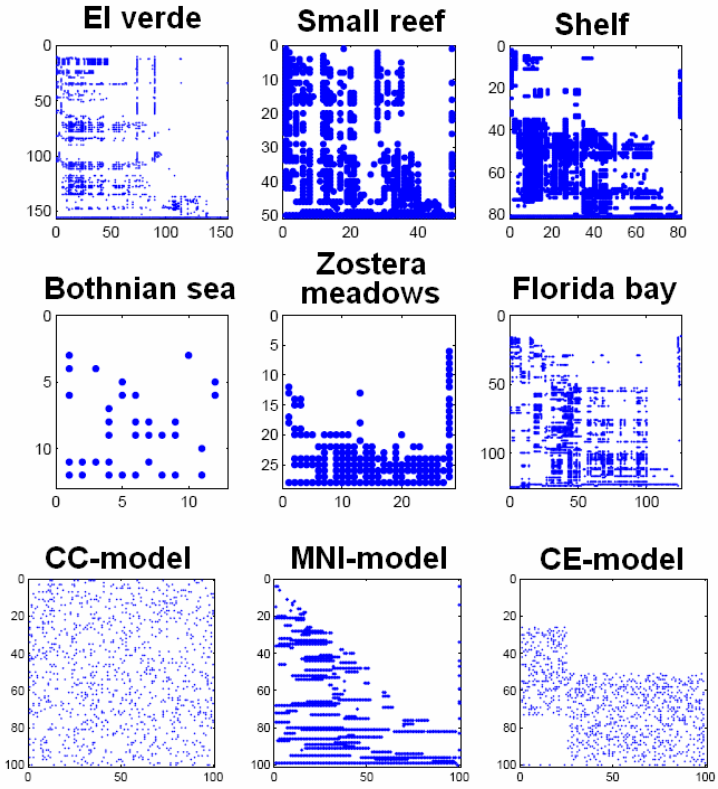

Figure 5: The spy plots (see Figure 4 for definition) for the constant connectance (CC) model, modified niche (MNI) model and cyber ecosystem (CE) model, compared to six empirical data sets.

All models were run to produce a great diversity of food webs. The models were analyzed and compared in terms of certain properties with their adjacency matrices. All models were scaled so that food webs with the same N and C values were compared among each-others in terms of their structural robustness (Paper I), and

in terms of how global energy cycling (Paper II), and stability (Paper III) scale with the complexity *NC* in the different model cases. These functional measures will be defined in the following sections.

3.7 Structural robustness in food webs

Paper I compares the models presented above (Box 5) in terms their structural robustness. In this context, *robust* means that the structural properties defined in Box 6 and 7 are relatively unaffected by random removal of single links/nodes. Box 6 summarizes the structural properties that are based on undirected graphs (ignoring the direction of the relations). Box 7 summarizes structural measures that are developed in order to also catch the directed properties of food webs.

A special focus is put on the pathways generated by decomposition and recycling of detritus. Since all species are assumed to contribute to the detritus compartment, this new structural component ensures that the food web is integrated into one strongly connected component, which also performs better in terms of efficiency (mean shortest distance between two nodes). The results show that the detritus compartment also makes the system more robust to link and node removal in terms of several of the measures presented in Box 6 and 7. The findings are especially important for sparsely interconnected networks (low *C*-values). Recycling of dead organic material makes food webs more integrated, and harder to disintegrate by small structural impacts.

Box 6: Undirected measures

Strongly connected components (N_s): A strongly connected component consists of all nodes that are directly or indirectly connected. In a fully integrated food web $N_s = 1$.

Bridges (N_b): A bridge is a connection whose removal causes the splitting of a strongly connected component into two separated components.

Cutpoints (N_c): A cutpoint is a node whose removal causes the splitting of a strongly connected component into two or more separated components.

Diameter (D): Average shortest path length taken over all node pairs $D = < d_{ij} >$.

Efficiency (E): Average of reciprocal path lengths $E = <1/d_{ij}>$, where $1/d_{ij}$ is defined if there is no path between i and j.

Box 7: Directed measures

Nodes that are part of any structural cycle (N_o): A node i is a part of a structural cycle if its position in the directed graph is such that a flow unit, leaving i, can return to i by following directed pathways.

Mean number of recipient nodes (N_r): If an energy unit leaves a node i, the number of recipient nodes is the number of other nodes it can it reach by following directed pathways from i.

3.8 Structural cyclicity in food webs

Food webs are structural diagraphs, showing not only which species are interlinked, but also the direction of the relation (energy transfer). The number of directed pathways of length $m>0$ between any node pair is found by raising the adjacency matrix to the m'th power (Borett et al. 2007). Pathway proliferation, developed as a measure of how the number of possible pathways between two nodes increases with path length, has further been used as a measure of the influence of indirect interaction in strongly connected networks. For large m, the rate between the number of pathways of length $m+1$ and m approaches the dominant eigenvalue, so that:

$$\frac{A^{m+1}}{A^m} \to \lambda, m \to \infty \tag{6}$$

Generally the increase of A^m with m will increase with the number of cycles in the system. The dominant eigenvalue of the adjacency matrix can be regarded as a measure of how well the structure of the graph supports cycling of matter/energy. The dominant eigenvalue (λ) is therefore called the *structural cyclicity*. λ is a purely structural measure, and does not measure the actual quantity of flow; and therefore differs from the Finn cycling index (Finn 1976).

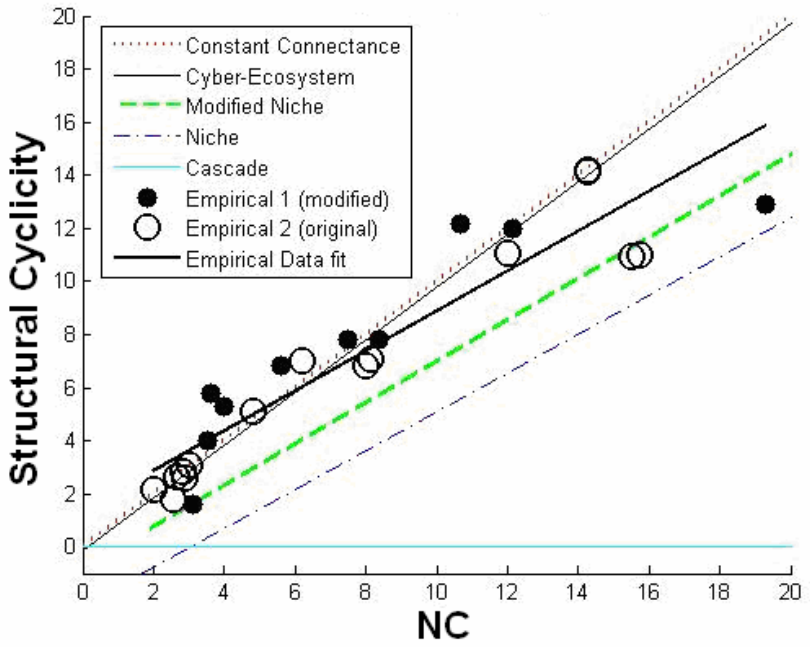

Figure 6: Structural cyclicity in five food web models, compared to empirical data. Regression lines for models are based on 1000 runs (for different values of N and C) with each model. Regression line for data is based on the data points shown in the figure.

Paper II compares the five food web models in Box 5 in terms of their structural cyclicity, and also compares the results to empirical food web data. In all models the structural cyclicity scales more or less linearly with the complexity (*NC*) of the webs, a trend also found for the empirical data sets as seen in Figure 6. The detritus compartment is found to increase the structural cyclicity. The modified niche model gave the best fit to empirical food webs.

Structural food web models aim at reproducing the structural features of food webs that are essential for their function. Paper II identifies structural cyclicity as one essential feature. The structural cyclicity is a measure of how well a food web structure provides a substrate for energy/matter cycling, but does not quantify the actual cycling. Due to energetic considerations, it is common to assume that the biomass decreases with the trophic level, since, as a rule of thumb, 90% of the energy is dissipated in every transfer. Hence, at the higher levels of the food web hierarchy, energy transfers will commonly be some orders of magnitude less than the transfers from primary producers. Since some pathways carry more energy/matter transfers than others, some cycles may be very important for the total cycling, while others will be less so. Unweighted models like those in Paper II can not capture such quantitative differences, and results based on structure alone may have limited validity (a further discussion on the quality of structure based results is found in Section 5.1). On the other hand, these structures are present in nature, and the modified niche model produces food webs that have a structural cyclicity in agreement with empirical food webs. Studies have also shown that the strength of a link is not always correlated to its importance for system stability (McCann et al. 1998; de Ruiter et al. 1998). In other words, a link is not necessarily unimportant because it is weak. With today's computational power at hand, there is no reason to discard structural features. General food web models should rather aim at reproducing as many empirically observed features as possible.

3.9 Dynamic stability in food webs

Paper III addresses system dynamics in an implicit way, inspired by the approach of May (1972). No assumptions are made on the underlying dynamic equations. A dynamic food web is assumed to have a fixed point attractor. A weighted community matrix (Ã) is constructed to describe the interactions and their strength in the vicinity of this fixed point. The community matrix represents the interaction coefficients when the dynamic system has been linearized around this fixed point. The criterion of neighbourhood stability (Box 3) was used as the dynamic stability measure. Eigenvalue analysis of the community matrix is used to check whether a perturbation from equilibrium will tend to increase (*i.e.*, it is further removed from equilibrium and is unstable) or decrease (*i.e.*, it is brought back to equilibrium and is stable).

Whereas May's original work was based on randomly generated communities, Paper III goes deeper into the specific importance of food web structure and distribution of interaction strengths. The structural food web models in Box 5 were transformed into community matrices relating the gain of a predator and the loss of a prey, as illustrated in Figure 7.

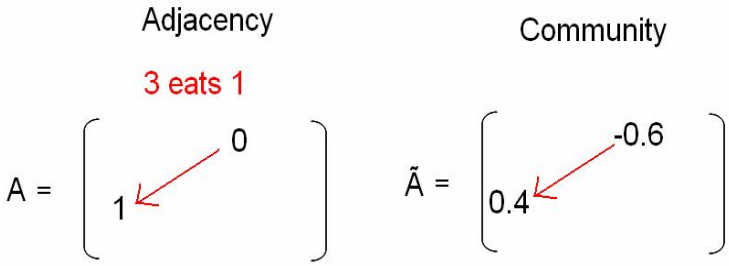

Figure 7: Example of how a predator-prey relation (1,0) in the structural adjacency matrix is quantified in the community matrix that contains matrix elements linking the predator gain and prey loss (+,–).

In May's work, the matrix elements in Ã were drawn from a normal distribution with mean zero and standard deviation *a*. This results in the approximate relation:

$$\sum_{i,j}\left|a_{ij}\right| = 0.8N^2Ca\,. \tag{7}$$

For direct comparison with May's results, all community matrices were normalized to satisfy the condition above. This means that the mean interaction in the system will be *0.8a*. For simplicity, *a* (and not *0.8a*) will still be referred to as the mean interaction strength. May showed that for randomly generated communities there is a steep threshold (for *a*), so that almost all food webs that satisfy

$$a < \frac{1}{\sqrt{NC}} \tag{8}$$

are stable, and almost all food webs that do not are unstable. May allowed all kinds of interactions, so that all the combinations $(\tilde{a}_{ij},\tilde{a}_{ji})$ = (0,0), (+,–), (+,+), (–,–), (0,+) and (0, –) could occur (the plusses and minuses here represent any positive and negative numbers determining whether a species gains or looses by the presence of the other species). This is referred to as the ecosystem-paradigm. The food web models, were constrained to only include predator-prey (+,–) interactions. As in May's work, the diagonal elements were chosen to be –1, meaning that the single species have a self-stabilizing effect (i.e. approaches carrying capacity) in their intraspecific interactions (May 1974).

The first main finding of Paper III is that food webs are more stable than ecosystems. This is most likely due to the destabilizing effects of positive feedback loops (+,+) and (–,–) (May 1974).

In a second analysis in Paper III, the interaction coefficients are drawn by ecologically inspired distributions defined by the predation intervals in the niche and modified niche models. In this case, the probability of a web being stable decreases more gradually with *a*, and there is no steep *a*-threshold (see equation 8)

between unstable and stable webs. In this case, stability depended strongly on the distribution of interaction strength (and not only on the mean value). A comparison of stable to unstable webs revealed that a few very strong links embedded in a majority of weaker links were beneficial for food web stability (Figure 8). Empirical findings support such a long tailed interaction strength distribution (Ulanowicz & Wolff 1991; Neutel et al. 2002).

The objective of Paper III was not to study food web stability on a general basis, but rather to see what aspects in a food web's structure and link distribution that is important for its function. For this, a functional measure was needed, and neighbourhood stability was chosen because of its mathematical simplicity. A distribution of a few strong links and many weak links has been found in several more complex modelling approaches (Kondoh 2003; Quince et al. 2005), but Paper III shows that such a link distribution is favourable also in terms of the criterion of neighbourhood stability.

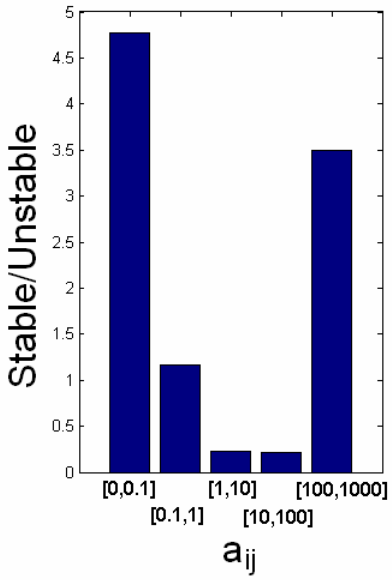

Figure 8: Link distribution in stable versus unstable webs. The x-axis show intervals of interaction strengths. The y-axis shows number of links in each interval in stable food webs divided by the number found in unstable webs.

Paper III does not reveal any correlation between neighbourhood stability and recycling of detritus, unless special assumptions are made on the strength of detrital pathways.

3.10 Structure versus dynamics in food webs

Structural robustness and dynamic stability are relevant at different time-scales. To start this brief commentary where the last section ended, recycling of detritus was not found affect neighbourhood stability in food webs (Paper III). On the other

hand, detrital pathways are of great importance for structural robustness (Paper I). If a food web is not dynamically stable it may (or may not: the analysis of this is not conclusive for neighbourhood stability) eventually result in a species going extinct, so that a node will disappear from the food web structure. If the system is not structurally robust, essential features of its organization will be changed by this node removal. This will in turn most likely have severe effects on system dynamics, possibly resulting in new species extinctions. The overlap between these two time scales is crucial in evolutionary and assembly models of food webs, but is not addressed in this thesis. Here, the focus is put on identifying the features in the structure and link distribution that play the most important role at each time scale respectively.

4 Neural network modelling

Descartes' characterization of mind as 'the thinking thing' (res cogitans) is finally abandoned. Mind is not a thing but a process – the process of cognition, which is identified with the process of life. The brain is a specific structure through which this process operates. The relationship between mind and brain, therefore, is one between process and structure (Capra 1997).

Neurobiology has reached quite far in describing the physiology of individual neurons (nerve cells) by studying them in isolation and manipulating the input in various ways (Reichert 1992). When a neuron is at rest, its internal potential is negative (–70mV) with respect to its surroundings. The cell membrane has different gating mechanisms, ion pumps and ion channels, which together establish the negative resting potential. When the resting potential is perturbed beyond a certain level (-55 mV), for example due to input from other neurons, the ion channels will open and close in a systematic manner, allowing fluxes of mainly ionic sodium, potassium (but also calcium and chloride) to pass through the nerve membrane. More then 50 years ago, Hodgkin and Huxley (HH) incorporated these mechanisms into a detailed description of a single neuron as a modified electrical circuit that transports electrical signals (Hodgkin & Huxley 1952). The HH-equations explain how a single cell can regulate flows of ions through its cell membrane in order to rapidly depolarize and re-polarize itself, changing its potential from rest (–70mV) to some positive value (often around +30mV), and back to rest again within a few milliseconds. This sudden and sharp change in potential generates a stereotyped pulse, an *action potential* (or spike), that travels along the axon (see Figure 9) of the neuron. The action potential is generated in an all-or-nothing manner, meaning that either the potential is fired with full amplitude, or not fired at all, resulting in almost identical spikes that can be regarded as binary information coding units.

However, an overall understanding of brain function does not seem to be embedded in a detailed description of its components alone. Complex neural networks have *emergent properties* which are not obvious from an understanding of neuron

physiology. The human brain consists of about 10^{11} neurons, and 10^{15} connections (Chklovskii et al. 2004). A biological neuron is composed of a cell body, called the soma, and of dendrites (input channels) and axons (output channels) that branch out of the soma (see Figure 9A). Neurons work as summing devices that sum up all their inputs, and depending on whether this sum reaches a certain threshold, respond by generating action potentials that become outputs to other neurons.

The inputs to a neuron will be either excitatory or inhibitory, meaning that they will either increase or decrease the receiver neuron's probability of firing a response signal (Reichert 1992). The brain processes information mainly by the transmitting of electric signals (action potentials) between millions of neurons across these nerve fibres. Most modelling approaches consider only a subset of these. The fundamental questions in understanding the brain, deal with how the activity of high numbers of interconnected neurons give rise to a global activity pattern that is somehow related to the function of the brain.

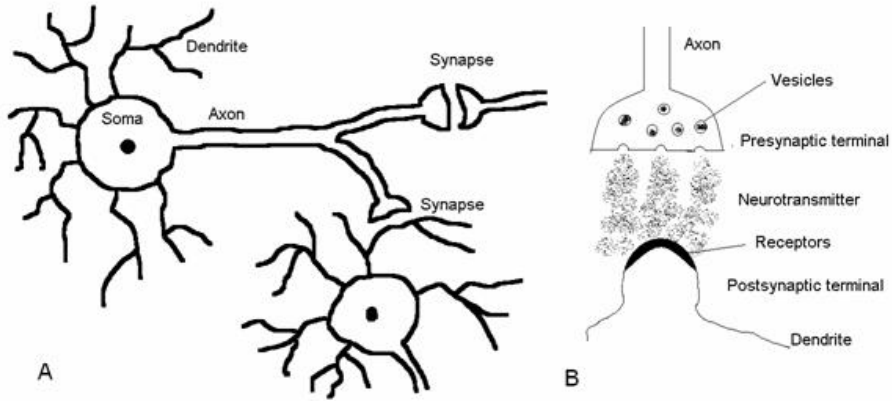

Figure 9: (**A**) A simple sketch of two neurons connected by a chemical synapse. (**B**) A sketch of a chemical synapse. Signals are transferred between two neurons via chemical neurotransmitters. The presynaptic part of the synapse contains neurotransmitters in so called vesticles. When a neuron sends an electrical pulse along its axon (output-channel), it causes a rapid change in presynaptic membrane potential that can make the vesticles open. The neurotransmitter will then be released in the synaptic cleft, where it binds to receptors on the postsynaptic part of the synapse, which in turn produces an electric input signal to the receiver neuron. (The illustrated example is canonical, and describes an axodendritic chemical synapse, which is the most typical. There are also dendrodendritic, axoaxonal and gap-junction synapses).

The brain needs to function in a complex and changing environment. This implies, among other things, to be able to respond and adapt to environmental events and changes at three different time scales (see Liljenström 1997):

- (T1): At the longest, evolutionary time scale, genetic adaptation has resulted in an initial and to some degree hard-wired connectivity of the individual neural network. However, recent studies suggest that electric ac-

tivity may still play some part in the structuring of the brain, also at the embryonic developmental stages (Spitzer 2006). The genome is believed to code for the basic rules for how the brain develops throughout life, in order to adapt to varying conditions and carry out various functions efficiently. However, genetic coding cannot account for the detailed synaptic and neural development during an individual's life. This slow evolutionary process is usually not considered in larger scale studies of neural networks which are directed towards understanding the brain as a real time information processing device.

- (T2): At an intermediate time scale, corresponding to the life span of an individual, the central nervous system adapts through numerous plastic mechanisms (Thickbroom 2007). Experiments have shown that neurons that are simultaneously active will be more likely to excite each others at a later stage, a phenomenon called long term potentiation (LTP) (Bliss & Lømo 1973). Long term depression (LTD) refers to the opposite phenomenon, where synapses between pairs of neurons that rarely operate in synchrony are weakened (Bear & Abraham 1996). Together, these processes may form assemblies of highly interacting and functionally associated neurons (Hebb 1949; Palm 1982; Bressler 1995; Varela et al. 2001; Fingelkurts & Fingelkurts 2006). This hypothesis of synaptic plasticity was early postulated by Hebb, who proposed that synapses (links) between co-active neurons will be permanently (or long lastingly) strengthened (Hebb 1949). Recent studies suggest that intrinsic plastic changes also occur (*e.g.*, changes of ion channel properties), and that synaptic plasticity is not the sole explanation of LTP and LTD (Debanne et al. 2003). In addition, ongoing structural plasticity, including the formation/elimination of synapses (sprouting/pruning), suggests that memory could also depend on these type of changes in the structural wiring diagram of the brain (Chklovskii et al. 2004).

- (T3): Finally, at the shortest time scale, fast, highly temporal changes in the neural activity are associated with the short term states of the brain, which in turn are closely related with cognitive processes (see *e.g.*, Freeman 1991; Seth & Edelman 2004).

The genetic processes at an evolutionary time scale (T1) and the plastic, adaptive processes at the intermediate time scale (T2) are not explicitly modelled in this thesis. They provide an implicit explanatory background for how cortical structures have developed, and how interaction strengths may change over time due to external stimuli or internal neural processes. The focus in this thesis in the shorter time scale (T3). The neural network models that are included in this thesis are used for investigating how different constructional features affect the neurodynamics in relation to electroconvulsive treatment, ECT (Paper IV) and anaesthetics (Paper V).

Larger scale measurements of brain dynamics are empirically accessible through techniques such as electroencephalography (EEG), positron emission tomography

(PET), and functional magnetic resonance imaging (fMRI). This thesis primarily refers to EEG studies. The EEG reflects the electrical activity of the brain, by recordings from electrodes placed on the scalp (or in some special cases, directly on the cortex). The resulting traces represent an electric signal that stems from a large number (thousands to millions) of neurons, and supposedly primarily from their postsynaptic potentials (the potential of the input signal to neurons). There is, however, still no consensus on the relation between EEG and the activity at the neuronal level (see *e.g.*, Freeman 1975, 2000).

4.1 Neural network objectives

Traditionally, there are two main objectives for using neural network models. One is to develop an understanding of real, biological neural networks (BNN), and the other is to develop computational tools, as artificial neural networks (ANN) which can be used for pattern recognition, optimization, associative memory, etc. (see Section 4.5 below).

This thesis is only concerned with the former, using computational models for BNN studies. The objectives here are summarized as:

- To develop different neural network models in order to study the physiological mechanisms behind the large scale dynamics (EEG) of the neocortex (Paper IV-V).

- To investigate how the flexibility of the EEG (in terms of diversity of dynamic features) depends on structural complexity of the model (Paper IV-V).

- To study how EEG features may be regulated by the density of interconnectedness at the network scale (Paper IV-V), and the density of ion channels at the single neuron scale (Paper V).

- To study the role that different network properties have on EEG-dynamics in relation to electro-compulsory treatment (ECT) of patients with major depression (Paper IV), and in relation to explaining possible mechanisms of anaesthetics (Paper V).

4.2 Clinical applications

EEG analysis is important in empirical research. Certain mental states or cognitive functions can be correlated to certain EEG patterns in different brain regions. EEG analysis is also of high clinical relevance, where it is used for determining consciousness states or mental health of patients. For example, different drugs and various (electric and other) treatments of mental patients are assumed to affect various neural mechanisms, and these can indirectly be studied using techniques such as EEG. Understanding the mechanisms behind EEG is crucial for linking brain function and brain dynamics. The computational models proposed in Papers

IV and V can serve as a step towards quantitative models that could be used to test the effects of different clinical treatments. A typical EEG setup and typical results are shown in Figure 10.

The neurodynamics of brain structures, as revealed by EEG, exhibit specific characteristic oscillation frequencies (Niedermeyer & Lopes 1999). The four major wave types are delta waves (up to 4 HZ) associated with deep sleep; theta waves (~4-8 Hz) associated with hypnosis and light sleep; alpha waves (~8-12 Hz), associated with a relaxed state of consciousness, and beta waves (~12-30 Hz) associated with active thinking. The frequency range ~30-100 Hz is referred to as gamma waves, is associated with higher mental activity, such as perception, problem solving, and attention. The brain activity is normally a blend of these frequencies, and the characteristic frequency spectrum changes with the age and mental state of the individual.

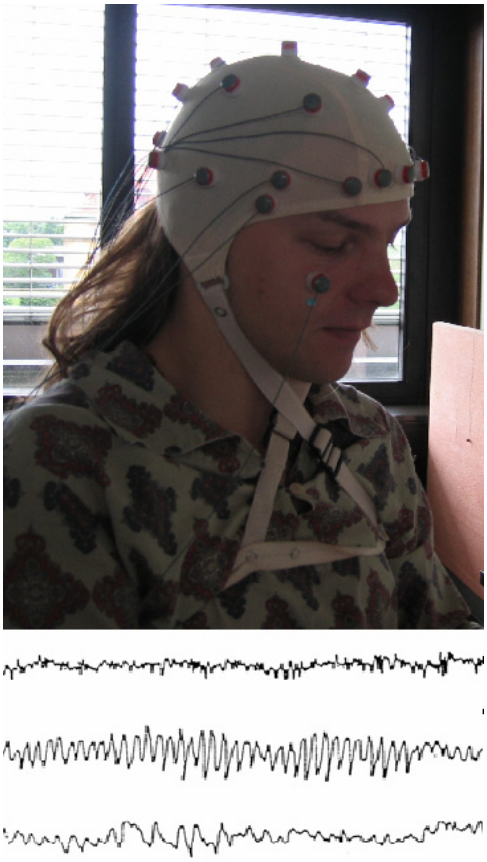

Figure 10: Instrumental EEG setup and characteristic EEG traces (picture taken from Wikipedia).

Electroconvulsive therapy (ECT) is today the most effective treatment against severe depression, yet the mechanisms behind the treatment are poorly known. EEG-data show that the dynamical activity patterns shift between several different

phases, as a response to an electric shock. Response patterns differ between individuals, and also depend on patient diagnosis and stimulus doses (Wahlund & Von Rosen 2003). Furthermore, correlations have been found between the response pattern and the efficiency of the treatment (West et al. 1999). Paper IV investigates three neural network models of different complexity in terms of their dynamic (EEG) response to an artificial electroshock, mimicking the ECT effect.

Anaesthesia works by setting the patient in a sleep-like state, characterized by slow waves in the EEG signal. One hypothesis is that some anaesthetics cause this effect by blocking specific potassium channels in the cell membrane of single neurons (Århem et al. 2003). Paper V applies a neural network model with details at the neuronal level to show how such selective blocking may cause phase changes in the global EEG.

4.3 Neural network structures

The brain seems to be evolutionary designed, at least partly, to deal efficiently with space, time, matter, and energy (see e.g. Liljenström 1997). Some studies suggest that the brain is organized to find an optimal balance between information processing and energy consumption, by reducing wiring costs and minimizing local travelling delays (see *e.g.* Laughlin & Sejnowski 2003). This does not imply that the brain is homogenous. On the contrary, the brain is highly heterogeneous, with many interacting subparts and regions.

Different brain regions are associated with different functional tasks. Different brain regions are also anatomically quite different, in the way neurons are interconnected, and in the composition of neuronal types. There is a relationship between the neuro-anatomical substrate (structural connectivity) and the spatial dependencies in activity patterns (functional connectivity) (Sporns et al. 2000).

There seems to be at least three basic architectural schemes at work in different regions of the brain (Buzaki 2007):

- The simplest uses strictly local wiring, so that only neurons that are closely located are connected to each others. This is typical for cerebellum, thalamus, and the basal ganglia. These regular networks form repeated modular circuits, where only neighbouring modules are likely to be connected. Because of this, computations are massively parallel.

- Another network type, which is rarer, has apparently random connections, where the probability of two neurons being interconnected is roughly independent of the distance. This kind of connectivity has so far only been found in recurrent excitatory circuits in the hippocampus.

- The third architectural scheme is typical for neo-cortex, and combines local modular connections with more random long range connections. This complex wiring scheme shows strong similarities with scale free and

small world networks (Box 1). For instance, an analysis of cortio-cortical connection data for different regions in the macaque and cat cortex has shown that these networks indeed are "small worlds" that also are connected in a close to optimal way, with respect to an efficiency measure on information exchange (Latora & Marchiori 2001). Another theoretical study has shown, using artificial neural networks, that the small world architecture is optimal for fast learning (Simard et al. 2005). However, other studies show that different structures may be optimal, depending on the computational task and the dynamics of the learning rules (Tsodyks & Gilbert 2004; Emmert-Streib 2006).

The idea that the functional units in the brain are not neurons, but rather typical microcircuits containing groups of neurons (locally repeated in a given brain area, similar to what is called network motifs in graph theory), has also gained attention. For instance, Shepherd has given an overview of the typical circuitry in different areas of the brain (Shepherd 1998). One of the neural network models in Paper IV is based on a simplification of the six layered neo-cortical microcircuit proposed by Shepherd (see Figure 11).

The human brain is often referred to as the most complex system in the universe, composed of a diversity of different neurons, synapses and electrical and chemical mechanisms. Neural network structures vary significantly over different brain areas, and little is still known about global connectivity patterns down to the level of individual neurons (Seth & Edelman 2004). Fortunately for modellers, much of the functionality of neural networks seems to be determined by large scale connectivity patterns and dynamics, rather than detailed local patterns (Liljenström 1991; Lansner & Liljenström 1994). Most modelling studies, including the ones in this thesis, focus on capturing and analyzing the significance of certain large scale aspects with the neuron-anatomy.

In Papers IV and V, computational neural network models of different structures were developed, in order to relate structural complexity to the stability and flexibility of the neurodynamics, as reflected in EEG. An emphasis was put on the role of large scale features such as the relation between excitation and inhibition, and network density.

4.4 Dynamic stability and flexibility in neural networks

Brain behaviour experiments have demonstrated that neural activity picked up by the EEG shows spatiotemporal transitions when the operation of behaviour switches (Fingelkurts & Fingelkurts 2006). Since certain features of the EEG are correlated with cognitive tasks or mental states, it is essential that the neurodynamics is stable to noisy fluctuations and common insignificant perturbations. At the same time it should be able to respond to weak signals such as an important sensory input, so that the neurodynamics (and accordingly the mental state) can switch to new states (Liljenström 2003). Electrophysiological evidence of brain flexibility comes from the variety of spatiotemporal patterns of neural and dendritic activity that are related to behaviour. Evidence for brain stability comes from

demonstrations that reproducible patterns recur in reproducible behavioural states (Freeman 2005).

Freeman proposed that chaotic dynamics are necessary for the brain to be able to respond rapidly and flexibly to its surroundings (Freeman 1991, 2000). Chaotic patterns are found in EEG readouts, and are not surprising in a highly complex system like the brain. Chaotic systems are known to be very sensitive, and can rapidly leap between different stable attractor states (see Box 3) if perturbed by an external signal, or between quasi-stable attractors by self organized dynamic processes associated to the phenomenon of chaotic itinerancy (Liljenström 1995; Tsuda 1996; Freeman 2003). This kind of sensitivity may be responsible for the brain's ability to switch between different states (Ashwin & Timme 2005). The multiple states collectively form a metastable collection of states of normal brain activity, each with its accompanying behaviour (Freeman et al. 2006).

In cortical networks, a dynamic balance between excitation and inhibition gives rise to an array of ordered or chaotic network oscillations (Freeman 2000; Brunel 2000). These activity patterns are not only affected by external sensory input, but are also due to the internally generated and continuously changing state of cortical networks. It has been suggested that the local-global wiring of cerebral cortex and the self organized complex dynamics that it supports are necessary ingredients for consciousness in the terms of subjective experiences (Århem & Liljenström 1997; Buzsaki 2007).

Many studies try to detect structures and mechanisms behind the EEG signal. Some characteristic features of the EEG are believed to stem from correlations in the firing patterns between pairs of neurons. It was recently found in studies of the vertebrate retina, that weak correlations between pairs of neurons coexist with strongly collective behaviour in the responses of ten or more neurons (Schneidman et al. 2006). Synchronized global activity patterns can rise from different underlying mechanisms, and common frequencies may be determined by synaptic or membrane time constants (Brunel 2000). Other findings show that coordinated network activity can emerge from single cells responding selectively to characteristic input frequencies, so that cells can be said to have a preferred resonance frequency (Hutcheon & Yarom 2000). For instance, in the visual cortex, synchronization between distinct areas are believed to be responsible for linking different features of the actual visual scene (Eckohorn et al. 1988; Gu & Liljenström 2007). Synchronization is also believed to be the mechanism responsible for the large scale integration of the brain activity into a unified cognitive moment (Varela et al. 2001). Dynamic features, such as resonances and phase locking between the activities of separated brain regions, have been early observed, and may be important drivers for linking different neural assemblies through the effects of synaptic plasticity.

4.5 Neural network models

One of the greatest challenges today is to understand the operations of cortical structures by relating global and local patterns of activity at time scales relevant for behaviour. Although certain features in the EEG signal are correlated with certain functional tasks, the relationship between structure, dynamics and the function of the brain is today poorly understood at a detailed level. Concepts such as stability and flexibility therefore have to be applied in a rather qualitative way (Liljenström 2003). Whereas food webs may be said to be dynamically stable if they have a fixed-point equilibrium or if no species go extinct, such simple definitions are only applicable in highly abstract and artificial neural network (ANN) models (Hopfield 1982; 1984).

Biological neural networks (BNN) are not steady state systems, but here, lesions and neuronal death may be considered as counterparts to species extinction in food webs. The global brain activity is continuous and changing, while single neurons may be active for periods, relax, and then become active again. Many dynamic BNN models are, in fact, complex attractor models, whose essential features are spatio-temporal patterns of activity, belonging to one of several attractor states that are robust in the sense that they are not critically dependent on the detailed functioning of individual neurons (Lansner & Liljenström 1994). Common for most BNN models, it seems essential that the global dynamics should be able to maintain certain characteristic features *without* reaching a static steady state. At the same time, the dynamics should be flexible so that the characteristic features may be altered by important external inputs or internal mechanisms (Liljenström 1997; 2003). The work of this thesis demonstrates how the stability and flexibility of neural networks are related to the density of connections (Paper IV & V), the balance between inhibition and excitation (Paper IV & V), and the density of ion channels on the single neuron level (Paper V).

Unlike most computer processors, the brain is highly parallel in its operation, and it is organized into several different brain regions occupied with different tasks at the same time. Another difference is that the brain is plastic and changes the strength of its connections (synaptic plasticity) over time, a process involved in memory and learning. Neural networks show amazing capabilities in solving specific tasks, such as pattern recognition and associative memory.

Artificial neural network (ANN) modelling has developed into a highly mathematical and statistical discipline, studying such networks as highly interesting computational tool in their own right. Although highly inspired by biological neuronal functions, many ANN models have become far removed from biological reality, as opposed to BNN models whose main aim is to simulate certain features of the real systems. Nevertheless, the boundaries between the fields are not always clear, and simplified ANN models are often used when trying to understand biological principles of organization. For overviews of ANN modelling, see Haykin (1994), or Jain et al. (1996).

The focus of this thesis is on BNN modelling. A large variety of different BNN models have previously been developed and applied. Most of these try to capture certain structural and dynamical aspects of the brain, in stead of reproducing the detailed (and largely unknown) anatomical varieties. BNN models are distinguished from each other by their different levels of sophistication at two organizational scales: 1) the dynamic equations that determine input-output relationships for single neurons, and 2) the structural description of the network. As in any modelling setup, the level of detail should be chosen with regard to the problem one wishes to investigate.

Model neurons range in complexity from the simple, binary McCulloch-Pitts neuron (McCulloch & Pitt 1943) to the biological realism and detail of the spiking HH-neuron (Hodgkin & Huxley 1952) with several structural compartments and features (see *e.g.* Bower & Beeman 1998). The HH-model is based on measurements on the giant squid axon, but has been successfully used (with small modifications) to describe other neurons types. The HH-model uses a set of four coupled differential equations to give a detailed and biologically realistic description on how the cell regulates its ion pumps and ion channels to produce the action potentials. Simplified network frameworks for spiking neurons have been developed by averaging the spiking effects over groups of neurons, and in this way reducing the HH-equations (Gerstner 2001).

Many neural network models have been developed to study how dynamically driven processes of synaptic plasticity may structure neural network, and how memory storage can be explained in terms of link distribution (see *e.g.* Hopfield 1982, 1984; Kohonen 1988; Siri et al. 2006). In such models, emphasizing learning rules and structural moulding, simple neural models may be sufficient since the detailed short term dynamics is not of particular interest. Simple modifications of the McCulloch-Pitts neurons have been applied in many studies, using continuous sigmoidal input-output relations (see *e.g.*, Hopfield 1984), so that

$$y = g(x) = 1/(1 + e^{-\beta x}), \tag{9}$$

where x is the summed and weighted input, and β is a parameter that determines the slope of the sigmoid curve. As opposed to the spiking HH-neurons, the continuous and abstracts relations can be interpreted as the average firing rate of a group of neurons, so that the network nodes are functional modules, representing larger groups of neurons. Although devoid of many details, such models are able to reproduces realistic spatiotemporal activity patterns of, for example, the olfactory cortex (Liljenström 1991).

The work presented in Paper IV & V models the EEG as a functional measure in itself, and specifically addresses mechanisms behind the EEG. For these studies, relatively complex and spiking neural models were applied.

4.5.1. Fitzhugh-Nagumo networks

Paper IV uses networks of Fizhugh-Nagumo (FN) neurons (Fizhugh 1961) to model how the EEG responds to artificial electric shocks (ECT) for different network structures. The FN-model (see Box 8) is based on the HH-model, but reduces the number of equations. Therefore, the equation parameters do not have the same clear biological interpretation as they do in the HH-formalism, where they describe detailed mechanisms at the single neuron scale. Still, FN neurons behave in a similar, spiking manner as HH-neurons, and seem to have sufficient complexity to allow for large scale dynamics studies.

The network model in Paper IV was inspired by the work of Giannakopoulos et al. (2001), using the same values for most parameters. However, the model was expanded by using different input terms for excitatory and inhibitory neurons (the two different sums in Box 8) so as to be able to regulate the balance between the two kinds of interactions.

Box 8: Dynamics for a network of excitatory (inhibitory) Fitzhugh-Nagumo neurons:

$$\tau^{ex(in)}\dot{u}_i^{ex(in)}(t) = -u_i^{ex(in)}(t) + p^{+}\sum_{k=1}^{n} c_{ik}^{ex(in)/ex}\, g(v_k^{ex}(t - T_{ik}^{ex(in)/ex})) - p^{-}\sum_{k=1}^{n} c_{ik}^{ex(in)/in}\, g(v_k^{in}(t - T_{ik}^{ex(in)/in})) + e_i^{ex(in)}(t - T^{\sigma})$$

$$\dot{v}_i(t) = c(w_i(t) + v_i(t) - \tfrac{1}{3}v_i(t)^3) + \gamma_i u_i(t)$$

$$\dot{w}_i(t) = (a - v_i(t) - bw_i(t))/c$$

u_i:	The postsynaptic potential of neuron *i*
v_i:	The membrane potential at the axon initial segment
w_i:	An auxiliary variable stemming from simplifications of the HH-formalism.
a, b, c:	Positive constants, appropriate for the existence of the oscillation interval.
g(v):	A nonlinear function for the relation between the pre- and postsynaptic potential.
e_i:	External input.
c_{ik}:	Connections (0 or 1) from *k* to *i*.
$p^{+/-}$:	Excitatory/inhibitory connection strengths.
$\tau^{ex/in}$:	Excitatory/Inhibitory time-constants.
T_{ik}:	Signal delay (synaptic + propagation delay) from neuron *k* to neuron *i*.
γ_i:	Synaptic membrane conductance of the neuron *i*.

4.5.2 Frankenheauser-Huxley networks

In order to study possible mechanisms behind the function of anaesthetics, Paper V uses a modified version of the HH equations, called the Frankenheauser-Huxley (FH) equations (Frankenheauser & Huxley 1964). Like the HH-model, the FH-model (see Box 9) incorporates a fine level of biological realism, and the density of active sodium and potassium ion channels in the cell membranes of single neurons can be regulated. This neural model makes it possible to vary the density of ion channels at the single neuron level.

The specific parameters for this neural model were taken from Johansson & Århem (1992). An equation for the signal transfer (the summation in Box 9) between

neurons had to be added to the original FH-equations. Signal transfers were modelled by letting the action potential in one neuron result in stereotyped, exponentially decaying inputs to all receiving neurons. Such transfer relations have earlier been used by Gerstner (2000), but for another framework that does not include FH-neurons.

Box 9: Equations for a network of Frankenhaeuser-Huxley neurons:

$dv_i/dt = (I_S - I_{Na}(v_i,m_i,h_i) - I_K(v_i, n_i) - I_L(v_i) + I_i)/C_M$
$dm/dt = \alpha_m(v)(1-m) - \beta_m m$
$dh/dt = \alpha_h(v)(1-h) - \beta_h h$
$dn/dt = \alpha_n(v)(1-n) - \beta_n n$

where

$I_{Na} = A_m P_{Na} (vF^2/RT) ([Na]_o - [Na]_i \exp(vF/RT))/(1-\exp(vF/RT))$
$I_K = A_m P_K (vF^2/RT) ([K]_o - [K]_i \exp(vF/RT))/(1-\exp(vF/RT))$
$I_L = (v - V_R)/R_M$
$P_{Na} = P^*_{Na} h m^2$
$P_K = P^*_K n^2$

$$I_i = \sum_j c_{ij} \sum_f 1/\tau_s \exp\left[(t - t_{syn} - t_j^{(f)})/\tau_s\right] \quad (t - t_{syn} - t_j^{(f)} > 0)$$

$$c_{ij} = c(d_0/d_{ij})$$

and where the symbols represent the following parameters and constants:

v	Membrane potential
$t, t_{syn}, t_j^{(f)}$	Time, synaptic delay, time of action potential f in neuron j.
τ_s	Synaptic time constant
I_S	Stimulation current
I_L	Leak current
I_C	Capacitive current
I_{Na}	Initial transient current
I_K	Delayed sustained current
I_i	Synaptic input to *i* resulting from all action potentials in all other neurons.
P_{Na}, P_K	Membrane permeabilities for Na^+ and K^+
m, h, n	Variables for P_N activation- (*m*), inactivation (*h*) and P_K activation (*n*)
α, β	Rate functions for *m*, *h*, and *n* as indicated by suffix. Definitions and values given in Johansson & Århem (1992)
P^*_{Na}, P^*_K	Permeabilities for Na^+ and K^+, when all Na and K channels are open (m s^{-1})
V_R	Resting potential (= $-70\ 10^{-3}$ V)
A_m	Membrane area ($100\ 10^{-6}$ m^{-2})
R	Gas constant (8.3143 J K^{-1} mol^{-1})
F	Faraday's constant (96.48701 C mol^{-1})
T	Absolute temperature (280 K)
C_M	Membrane capacitance (7pF = 7μF/cm^2 = $7\ 10^{-2}$ F m^{-2})
R_m	Leak resistance (4.3GΩ = 4.3 kΩ cm^2 = $4.3\ 10^{-1}$ Ω m^2)
Na_i, Na_o	Intra- and extracellular Na concentrations (14 and 114.5 mmol/l = mol m^{-3})
K_i, K_o	Intracellular and extracellular K concentrations (120 and 2.5 mmol/l = mol m^{-3})
c_{ij}	Connection weight between neuron *i* and *j*.
d_0, d_{ij}	Nearest neighbour distance, distance between neuron *i* and *j*.
c	Global density parameter (connection strength)

4.6 Simulations with neural network models

All the work on neural network modelling presented in this thesis follows the same logic, described by the following four steps: 1) Computational neural network models were programmed in Matlab. 2) Dynamic equations for the input-output relations for single neurons, and for the signal transfer between neurons were specified. 3) The global dynamics of the system was a model of the EEG-signal, and was defined as the arithmetic mean membrane potential taken over all neurons. 4) Several simulations were run for different choices of model parameters (representing structural characteristics of the network, or some neurological mechanisms), in order to investigate the effect of different parameters on the EEG signal (functional measure).

In both the FN and FH models (Box 8 & 9), the entire structures of the networks were determined by the sets of connection weights c_{ij}, being zero for unconnected nodes, and having some weighted value for all connected node pairs, depending on their spatial positions with respect to each other. The model weights give a negative input for inhibitory synapses, and a positive input for excitatory synapses. When simulations were run, the network dynamics was driven by an external input, representing a noisy background signal (Paper V) or a continuous input (Paper IV) that could stem from some other brain region outside the system boundaries. This driving input initiated dynamic signalling between all the neurons in the network.

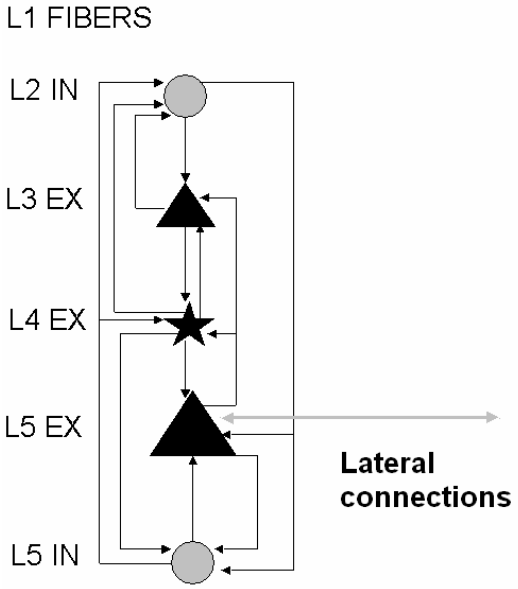

Figure 11: Six layered unit oscillator of excitatory (EX) and inhibitory (IN) neurons, connected to other oscillators through lateral connections between neurons in layer five.

In Paper IV, the following parameters were varied: 1) The relative number of inhibitory vs. excitatory neurons, 2) the relative strength of inhibitory versus excita-

tory synapses (p^+ and p^- in Box 8), and 3) the entire network structure, using three different structural models, ranging from a simple pair oscillator model to a highly complex and anatomically inspired structure. In this way, the importance of these parameters for the flexibility in the ECT-response was studied. For illustration, one of the neural network structures of the models in Paper IV is shown are in Figure 11.

In the dynamically more complex FH-model of Paper V, the network structure was limited to a simple regular lattice of 6 × 6 neurons with distant dependent connection strengths between neuronal pairs, $c_{ij} = c(d_0/d_{ij})$, as described in Box 9. Simulations were run with exclusively excitatory networks, and with mixed networks where 6 of the 36 neurons were inhibitory, as illustrated in Figure 12. For both cases, density dependent regulatory mechanisms were modelled at two different scales. This was done by running different simulations with variations in the following parameters: 1) The global connectivity (c) regarded as a density parameter (since connection strength decreases with distance), and 2) the density of ion channels on the single neuron level. A possible effect of anaesthesia was modelled by blocking (decreasing the density of) specific inhibitory potassium channels.

Despite realistic parameter values in terms of distances, the time constant, neural mechanisms, and the relative number of excitatory and inhibitory neurons, the neural models applied both in Paper IV and Paper V are freely parameterized in terms of interaction strengths. This is true for most neural network models, since there is no way, as yet, of measuring and parameterizing synaptic strengths in brains *in vivo*. In Paper IV, connection weights were tuned in relation to the external input until the network gave rise to a realistic global activity pattern. After this initial tuning, the connection weights were only varied collectively in terms of defined parameters for global inhibition/excitation. In Paper V, all connection weights were restricted to follow the same distance dependent relation.

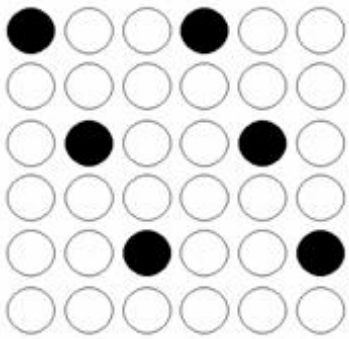

Figure 12: Network of 6 × 6 FH-neurons. 6 neurons (black) in the grid can be made inhibitory to compare the difference between purely excitatory networks and mixed networks. In the neo-cortex about 20% of the neurons are inhibitory. The number 6 (as opposed to 7) was chosen out of symmetry reasons.

4.7 Phase shifts in neural network dynamics

Electroconvulsive therapy (ECT) is today the most effective treatment against severe depression. The patient EEG evoked by ECT stimulation generally exhibits a specific pattern of seizures in the central nervous system, characterized by several (6-7) post-ECT phase-shifts. The mechanisms behind this response pattern are poorly known. Paper IV hypothesized that the cortical network structure and specifically the balance between excitation and inhibition could carry us a long way in understanding them.

In Paper IV, neural network models were parameterized so that they exhibited stationary dynamics when driven by a continuous external input. An artificial electric shock, simulating electroconvulsive therapy (ECT), was given to the system. The ECT response in the EEG signal can undergo phase shifts, such as observed in Figure 13. The ECT response is characterized by decaying, high amplitude oscillations, going over to slow wave oscillation, and finally, going over to more enveloped network activity. This suggests that these models, based on simplified, but anatomically inspired structures, capture some of the most important mechanisms involved in generating the neo-cortical EEG signal and its response to ECT. The features of the response were found to depend strongly on the complexity of the network and in particular on a delicate balance between excitation and inhibition. The number and interaction strength of inhibitory neurons were found to be crucial for producing the most flexible (and clinical-like) response. In addition, a combination of strong local connections and weak global connections gave rise to the most flexible dynamics.

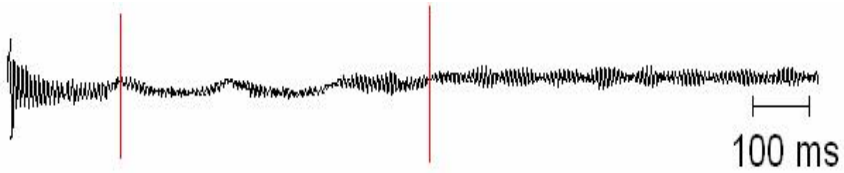

Figure 13: Phase shifts in a neural network dynamics after artificial ECT-stimulus.

Three models of different complexity were used. Phase shift responses were only observed in the two most complex ones. These were in turn only able to reproduce 2 of the 6 clinically observed phase shifts. The phase shifts occur in the transient system dynamics before it reaches a stationary attractor. This transient period is likely to depend strongly on the model complexity, and the observed trend suggests that more complex models, including larger cortical areas, could explain the high number of clinically observed phase shifts. On the other hand, delayed effects may also stem from different mechanisms than the short range balance between inhibition and excitation. These may be due to long range signalling between other parts of the brain (not considered in our network model of limited spatial scale) and delayed release of neuromodulators.

4.8 Density effects in neural networks

Part of the work in Paper V was aimed at finding useful qualitative classifications of EEG features. Clinical EEG is flexible in switching between different classes of dynamics. In Paper V different underlying mechanisms that might be responsible for these switches are studied. Results from different simulations were compared qualitatively by classifying the EEG-signal into one of the states A-D in Figure 14.

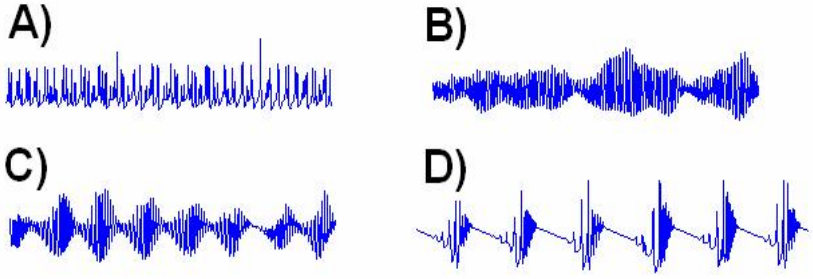

Figure 14: Qualitative classifications states of different EEG features: **A**) spiking activity, **B**) enveloped activity, **C**) enveloped activity with dominant slow wave frequency, and **D**) bursting activity.

Changes, both in synaptic strength and in membrane currents on single neurons, will result in different response patterns to an input (Sharp et al. 1996). In Paper V, the relationship between these two mechanisms is studied at a network level. It was found that the flexibility of the neuro-dynamics depends on a fine balance between the network density (at the global scale), and the ion channel density (at the nodal scale). Changes in density at two different scales could drive the EEG signal between qualitatively different states. For instance, the EEG might be driven from an irregular, enveloped activity pattern (Figure 14B) to an activity pattern with characteristic slow wave frequencies (Figure 14C), either by increasing the network density (mean synaptic strength), or by decreasing the density of inhibitory K-channels at the single neuron level. The former may be realized through activity driven synaptic plasticity. The density of ion channels can supposedly be altered by the neuron itself as a response to some cue (Destexhe & Marder 2004; Debanne et al. 2003) or by pharmacological means.

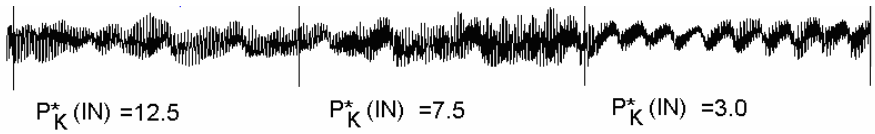

Figure 15: Changes in mean network dynamics (EEG) caused by decreasing the density of potassium channels in inhibitory neurons.

Selective blocking of specific K-channels have been hypothesized as one of the main function of some anaesthetics (Hille 2001; Århem et al. 2003). Paper V shows that selective blocking of inhibitory K-channels may very well drive the dynamics of a neural network into slow wave oscillations (see Figure 15) which are characteristic for anaesthesia (and sleep).

The similarities between the simulation results in Papers IV & V and clinical EEG are qualitative. The results are suggestive on the most important neural mechanisms underlying the EEG signal, and captures qualitative features of its response to ECT and anaesthesia. Hopefully, future development of models of this kind may be more quantitatively fitted to patient data, and be used as clinical tools for further understandings of EEG and ECT mechanisms. Simulations with such models could experiment with different doses of drugs and ECT, as well as with different ECT frequencies.

4.9 Large scale neurodynamics and the mechanisms behind

The large scale neurodynamics (EEG) is correlated to the cognitive state. However, it has been a matter of debate whether the neurodynamics is of importance in itself as the physiological aspect of mind. It might be the processes underlying the EEG signal that are of real importance, whereas the EEG in itself is just a by-product. Paper V demonstrates explicitly how different underlying processes at two different levels of organization qualitatively can give rise to similar features in the EEG. If changes in network density can cause similar state switches as changes in ion channel density at the neuronal level, the large scale dynamics does not conclusively reveal its underlying process.

5 General Discussion

5.1 Quality of results

It has been argued in several occasions that purely structure-based studies as in Paper I and II are not sufficient to understand biological networks (Arita 2005; Wetiz et al. 2007). Even if measures of robustness and structural cyclicity are highly suggestive of which structural principles are important in nature, they are in most cases not conclusive in terms of how they affect system dynamics where energy transfers and flows vary over time.

The strength of structural studies is the generality of their application. Since structural information on biological systems is far easier to access than any quantitative dynamical information, and since the models are based on few quantitative assumptions, they do provide a useful first step towards understanding the basics of biological networks. In addition, structural models work as the substrate for system dynamics. Reproducing realistic biological network structures should be the first step in any attempt to gain a full understanding of these systems.

Dynamic network models simulate the time development of the system in a quantitative way. However, biological systems are highly complex, meaning that many parameters in the equations are unknown. In any model, the systems must be sim-

plified and many parameters are based on reasonable assumptions, often introduced stochastically.

This thesis does therefore not aim to fit network models to data in any quantitative way. Rather, it proposes certain underlying principles (such as the structural algorithms in food web models, the regulations of ion channels in single neurons, or changes in the global network density) as hypothesises of generic properties that are important for the function of biological networks. The model simulations provide qualitative answers to whether these hypotheses are possible explanations to the system function. In this way, the thesis offers insight into which system mechanisms may be important. Even if they lack a detailed predictive power, analysis like this can reveal that there are critical thresholds, attractor states and critical balances in the systems, and they can identify which model parameters are most important for the function of the system. In this way, the models in this thesis give empirical scientists guidance in what they should look for.

5.2 Density effects and the relationship between scales

It was argued in Section 2 that the mean interaction strength in the network could be regarded as a density effect. The findings in paper III, IV and V all suggest that the diverse nature of biological networks is found at intermediate network density where the activity patterns arise from an interplay between the local effects of single nodes (or oscillatory units), and the global interactions. An exhaustive study of the importance of network density would require a theoretical model setup, aimed at drawing general conclusions on the balance between local and global effects. The more system specific approach that is found in this thesis has its value in assigning specific biological meaning to the concept of network density.

Consider the community matrix for a food web. Paper III used diagonal elements equal to –1. In the limit of no interactions (mean interaction strength $a=0$), the system is stable, due to the self-stabilizing form of each isolated species. The biological system would then be interpreted as a set of primary producers stabilized at their carrying capacities. Then, the interactions are "switched on". For $a<<1$, the food web is stable. For $a>>1$, the food web is always unstable (except in the case of complete anti-symmetry), meaning that the strong interactions dominate over the intrinsic stabilizing properties of the single species. The structure and link distribution of food webs are of importance for structural stability only for intermediate a-values, suggesting that the complexity of nature has been forged by an interplay between local and global effects.

Similar results were found when system dynamics was studied more explicitly in neural networks. Paper V shows that the flexibility of neuro-dynamics is most prominent for intermediate network density. In Paper IV, the most flexible (and realistic) ECT-response was obtained when the lateral connections (connecting unit circuits to each others) were relatively weak in comparison to intra-circuit connections.

The most explicit study of single node effects vs. network effects is presented in Paper V. The density of sodium and potassium channels in the neural membrane determines the characteristics of a neuron's response patterns to voltage fluctuations, and hence its intrinsic activity. For low global interaction strength, the system dynamics is determined by intrinsic node properties. When increasing the density of nodes (i.e. the global interaction strength) gradually, starting from zero, the global activity pattern changed from being determined solely by the sum of intrinsically spiking nodes towards a more synchronized network-determined activity. For high connection density, the network undertook bursting activity, with characteristic features that depend little on the properties of the single nodes. For intermediate interaction strength, the system dynamics was most flexible, in the sense that the dynamic features could be quantitatively changed by small changes, either in the ion channel densities of single nodes, or in global connectivity.

In Papers III-V, a fine balance between some local stabilizing effect and some global destabilizing effect gave the most realistic system response.

In summary, the structure and interaction strength distribution in food webs are only important for their dynamic stability if such a sensitive balance exist. Likewise, the balance between stability and flexibility of neuro-dynamics was shown to depend on a fine balance between local stabilizing mechanisms (in single neurons or unit circuits) and global connection strength, driving these units in and out of phase.

An analytically conclusive study of the relationship between the local and global scale, could be addressed by idealized and theoretical network models. The three model studies of this thesis have their strength in that they demonstrate qualitatively how different properties of two different kinds of biologically inspired networks depend on a sensitive balance between local intrinsic effects, and the strength of global interactions.

5.3 Dynamic & structural node diversity

One of the common simplifications in dynamic network studies is to assume that all the nodes are intrinsically identical. This means that all the equations have the same functional form, and that the heterogeneity in the network is solely due to the connections and their weights. For instance, food web models have shown that by allowing a subset of the species to be adaptive predators (regulating their diet towards abundant species) tend to stabilize the system (Kondoh 2003; 2006).

In Paper V, node diversity was introduced in a neural network by letting the subgroup of inhibitory neurons be intrinsically different than the majority of excitatory neurons. In this case it was shown that the network consisted of two subsystems that dominated at different global activity levels, showing that the flexible responses in the neuron-dynamics can be explained by switches between dominant sub-groups of neurons.

The detritus compartment was not found to have any effect on the dynamic stability of food webs unless special assumptions were made on the strength of the detritus links relative to other links (Paper III). On the other hand, the detritus compartment made the system significantly more structurally robust to severe system perturbations, such as link and node removal, representing effects at a longer time scale. This illustrates the possibility that different aspects of food webs may be responsible for systemic stability related to different events at different time scales.

5.4 The stability/flexibility dilemma

Stability and flexibility are two positively charged concepts. They still seem to be in some kind of opposition to each others, perhaps not as antonyms, but at least in the sense that it could be expected to be a trade-off between the two. In the system perspective, stability often refers to the system's ability to maintain some important features as they are. This works for food webs, which unarguably can be said to be stable if all species populations remain at fixed sizes.

The interplay between stability and flexibility is clearer when these concepts are considered in relation to the surroundings. The requirement of flexibility in neurodynamics is obvious when one realizes that the brain needs to deal with different tasks under different conditions. The meaning of stability and flexibility in the dynamics of a neural network is explained at a larger scale, in terms of their function for the survival and well being of the organism that owns the brain. This broader context contains the set of different challenges that a person is likely to face during a lifetime. The multiple states that the brain can switch between collectively form a *metastable* collection of states of normal brain activity, each with its accompanying behavior (Freeman et al. 2007). It thus seems that flexibility at one scale is a way of obtaining (meta)stability at a larger scale.

Food webs are living systems studied at the largest scale. This may be the reason why the concept of flexibility rarely shows up as a large scale measure in the food web literature, although a certain degree of flexibility is implicit in some studies of food web resilience (McCann 2000). It is difficult to picture a set of different external condition to which a food web as a whole should have a set of different response mechanisms, at least at time scales relevant for management issues. Seasonal variations could be one possibility, yet the abstract large scale food webs considered in this thesis normally map interactions in terms of annual averages.

When the concept of flexibility shows up in the food web literature, it is normally at the species level. For instance, species flexibility in terms of adaptive foraging, where predators direct their efforts towards abundant rather than endangered preys, has been found to stabilize food webs (Kondoh 2003, 2006). Also in these studies, stability seems to be the large scale goal, while flexibility at a more local level is a means of achieving it. Although flexibility might very well be studied theoretically in terms of a food web's ability to leap between different attractor states, the external events that could trigger such responses would most likely in-

volve significantly longer time scales than those considered in management issues. It is also hard to imagine that such leaps between global attractor states, causing fundamental changes, would be anything but disastrous for many of the organisms involved, including human beings. Food webs are therefore most commonly studied in terms of several different measures of stability, reflecting human values of conservation and sustainability, and perhaps also an idea of nature as ideally well balanced and constant. However, effects of global warming and habitat degradation may call for a new paradigm, searching for critical thresholds in the systems, and the characteristics of dynamic attractor changes.

5.5 Main contributions

The main contributions of this thesis are summarized below:

5.5.1 Food web conclusions

- Detritus alters generalizations of the structure and function of food webs. Detrital pathways increase the structural cyclicity and the structural robustness of food webs.

- Food web structure and distribution of interaction strength are of comparable importance for dynamic stability of food webs.

- Systems constrained to contain only antagonistic (+,–) interactions (food webs) are more stable than systems where all sorts of interaction pairs are allowed (ecosystems).

- Neighbourhood stability is optimized in food webs that are characterized by a few strong interactions embedded in a majority of weaker interactions.

5.5.2 Neural network conclusions

- A fine balance between inhibition and excitation is crucial for a flexible and realistic EEG response to clinical treatments with anaesthesia and ECT.

- Intermediate network density (i.e. where intrinsic node properties and global network interactions are of comparable importance) is optimal for flexible neurodynamics.

- State transitions in network neurodynamics can be evoked by regulatory mechanisms at two different scales: changes in cellular ion-channel density or changes in global interaction strength.

- Computational neural network models based on simplified, but anatomically inspired structures are able to capture some of the most important

mechanisms involved in generating EEG-signal and its response to anaesthesia and ECT.

5.5.3 Theory development

- The concepts: *Structural principles, structural complexity, interaction diversity, node diversity* and *network density* are proposed and defined. This set of constructional concepts provides a useful toolbox for biological network studies in general. Applications to food web and neural network models demonstrate that these concepts are crucial for the function of biological networks.

- The most interesting and realistic features of biological networks emerge at an intermediate network density. Network functions depend on the interplay between intrinsic node effects and effects of interactions at the network level. At an intermediate network density, the function of the network is particularly sensitive to *structural principles, structural complexity, interaction diversity* and *node diversity*.

- The *modified niche model* is novel for this work. In the line of simple structural food web models that only take network size and connectance as input parameters, the modified niche model is the first to explicitly include a detritus compartment. This model can be used in future studies.

- Frameworks for networks of interacting Fitzhugh-Nagumo and Frankenheauser-Huxley neurons have been developed, and can be used in further studies for investigating different aspects of EEG time series.

All models were programmed in Matlab, without using pre-defined toolboxes. For details on the program codes, please contact Geir Halnes: geir.halnes@bt.slu.se.

5.6 Personal comments and future prospects

As the reader may have noticed, the papers included are not arranged in a chronological order. My work as a PhD started with neural network models, under the supervision of Hans Liljenström. His expertise in this field defined the focus of study for the first half of my PhD, resulting in Papers IV and V. A stipend from Formas allowed me to spend three months at the International Institute for Applied System Analysis (IIASA) in Vienna, where I had the privilege to do a project under the supervision of Brian D. Fath. The project was awarded with a grant that allowed me to spend three additional months at IIASA. Fath's expertise in ecological network analysis defined the focus of study for the second half of my PhD, resulting in Papers I-III.

The initial plan was to move gradually from these first projects and into the field of ecology, bringing along neural network models as a toolkit. A concrete idea on how to realize this involved using artificial neural network (ANN) models as decision making devices for adaptive foragers, or for females selecting mates, acting

within a specific ecological context. The relevant field experiments required to complete the planned projects did, however, not receive funding. Still, the interface between the cognition of single organisms and their role in a larger ecological context has been rather poorly explored, and I believe that there are great future prospects for models of this kind. Such meso-scale models can be used to study the interplay between learning and evolution, and the importance of adaptation at different time scales.

Another idea, concerning my transfer from neural network modelling to food web modelling, was that the network abstraction allows theory to be easily transferred between fields. There are many examples of network theoretical measures being applied across system boundaries. For instance, the same graph theoretical measures can be applied to all systems described as networks (see *e.g.*, Strogatz 2001; Albert & Barabasi 2002).

A wide range of functional tasks have been studied in neural network models, where concepts such as synchrony, adaptation, flexibility, associative memory, classification and stochastic resonance (just to mention a few) have a specific meaning. In the network abstraction, all functional concepts are manifested as structural, dynamic and evolutionary network properties. Hence, via the network abstraction, these concepts can be projected onto other systems, where their biological meaning would have to be reinterpreted. It is my conviction that at least some of these concepts might be applicable to food webs and reveal new aspects of these systems. However, it appeared essential to become familiar with the existing theory in ecological modelling before doing any attempt to introduce new methodology to the field. Still, the prospects of transferring network concepts between fields appeal to me.

From a personal point of view, the broad scope of this thesis and the opportunity to work within two different fields has been very exciting. The different projects that I have been involved in, so far, have provided me with a methodological tool box that can be applied in later studies, which are anticipated in several pending project proposals.

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